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L2: Entry 1 of 14

File: PGPB

Aug 28, 2003

PGPUB-DOCUMENT-NUMBER: 20030162816  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20030162816 A1

TITLE: Method of treating metabolic disorders, especially diabetes, or a disease or condition associated with diabetes

PUBLICATION-DATE: August 28, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gatlin, Marjorie Regan	Hoboken	NJ	US	
Ball, Michele Ann	Morris Plains	NJ	US	
Mannion, Richard Owen	Mount Arlington	NJ	US	
Karnachi, Anees Abdulquadar	Hillsborough	NJ	US	
Guitard, Christiane	Hagenheim		FR	
Allison, Malcolm	Basel		CH	

US-CL-CURRENT: [514/342](#); [514/369](#), [514/563](#), [514/592](#), [514/635](#)

## ABSTRACT:

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide (I) 1

or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition; the use of such combination or composition for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; the use of such combination or composition for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; and to a method of improving the bodily appearance of a warm-blooded animal.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
Draw	Desc	Image									

☐ 2. Document ID: US 20030139434 A1

L2: Entry 2 of 14

File: PGPB

Jul 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030139434  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20030139434 A1

TITLE: Combinations comprising dipeptidylpeptidase-iv inhibitor

PUBLICATION-DATE: July 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Balkan, Bork	Madison	CT	US	
Hughes, Thomas Edward	Somerville	NJ	US	
Holmes, David Grenville	Binningen	NJ	CH	
Villhauer, Edwin Bernard	Morristown		US	

US-CL-CURRENT: 514/275; 514/3, 514/342, 514/343, 514/369, 514/423, 514/470, 514/492,  
514/563, 514/592

ABSTRACT:

The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, .alpha.-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and .alpha..sub.2-adrenergic antagonists, for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KMC
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☐ 3. Document ID: US 20030139429 A1

L2: Entry 3 of 14

File: PGPB

Jul 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030139429  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20030139429 A1

TITLE: Combinations

PUBLICATION-DATE: July 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cohen, David Saul	New Providence	NJ	US	

US-CL-CURRENT: 514/263.22

## ABSTRACT:

The present invention relates to a pharmaceutical composition, comprising

- (a) a phosphodiesterase 5 inhibitor or a pharmaceutically acceptable salt thereof and
- (b) at least one of the active ingredients selected from the group consisting of
  - (i) an anti-diabetic agent;
  - (ii) HMG-Co-A reductase inhibitors;
  - (iii) an anti-hypertensive agent; and
  - (iv) a serotonin reuptake inhibitor (SSRI)

or, in each case, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The pharmaceutical composition may be employed for the treatment of sexual dysfunction, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridemia, diabetes, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, syndrome X, erectile dysfunction, coronary heart disease, hypertension, especially ISH, angina pectoris, myocardial infarction, stroke, vascular restenosis, endothelial dysfunction, impaired vascular compliance, congestive heart failure.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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KMC

☐ 4. Document ID: US 20030114469 A1

L2: Entry 4 of 14

File: PGPB

Jun 19, 2003

PGPUB-DOCUMENT-NUMBER: 20030114469  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20030114469 A1

TITLE: Combinations

PUBLICATION-DATE: June 19, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cohen, David Saul	New Providence	NJ	US	

US-CL-CURRENT: 514/263.22

## ABSTRACT:

The present invention relates to a pharmaceutical composition, comprising

- (a) a phosphodiesterase 5 inhibitor or a pharmaceutically acceptable salt thereof and
- (b) at least one of the active ingredients selected from the group consisting of
  - (i) an anti-diabetic agent;
  - (ii) HMG-Co-A reductase inhibitors;
  - (iii) an anti-hypertensive agent; and

(iv) a serotonin reuptake inhibitor (SSRI)

or, in each case, or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier. The pharmaceutical composition may be employed for the treatment of sexual dysfunction, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridemia, diabetes, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, syndrome X, erectile dysfunction, coronary heart disease, hypertension, especially ISH, angina pectoris, myocardial infarction, stroke, vascular restenosis, endothelial dysfunction, impaired vascular compliance, congestive heart failure.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
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☐ 5. Document ID: US 20030114389 A1

L2: Entry 5 of 14

File: PGPB

Jun 19, 2003

PGPUB-DOCUMENT-NUMBER: 20030114389

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030114389 A1

TITLE: Combination of organic compounds

PUBLICATION-DATE: June 19, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Webb, Randy Lee	Flemington	NJ	US	

US-CL-CURRENT: 514/19; 514/342, 514/369, 514/592, 514/629

ABSTRACT:

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof and at least one antidiabetic agent.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
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☐ 6. Document ID: US 20030078269 A1

L2: Entry 6 of 14

File: PGPB

Apr 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030078269

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030078269 A1

TITLE: Biguanide and sulfonylurea formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus

PUBLICATION-DATE: April 24, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pearson, Don C.	Lakewood	WA	US	
Richardson, Kenneth T.	Anchorage	AK	US	

US-CL-CURRENT: 514/251; 514/474, 514/553, 514/561, 514/630

## ABSTRACT:

The invention describes formulations that include either metformin, sulfonylurea or a biguanide-sulfonylurea combination as one active ingredient in addition to specific, other active ingredients. The compositions and dosage forms of the invention are clinically useful as methods for increasing the effectiveness, efficiency and safety of the included biguanide (metformin) and/or sulfonylurea in the prevention and treatment of insulin resistance and diabetes mellitus. The carefully chosen additional active ingredients of the invention are designed in a modular fashion to prevent and rectify adverse events associated with insulin resistance syndrome and diabetes mellitus, and those adverse incidences associated with the concurrent use of metformin and/or the sulfonylureas. When clinically administered, the invention will provide therapeutic levels of metformin and of a sulfonylurea, alone or in combination, and broaden their usefulness. The invention will retard the progression of insulin resistance to type 2 diabetes, and reduce the serious microvascular and macrovascular complications commonly associated with insulin resistance syndrome and diabetes mellitus.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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KMC

☐ 7. Document ID: US 20030077335 A1

L2: Entry 7 of 14

File: PGPB

Apr 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030077335

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030077335 A1

TITLE: Formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus

PUBLICATION-DATE: April 24, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Richardson, Kenneth T.	Anchorage	AK	US	
Pearson, Don C.	Lakewood	WA	US	

US-CL-CURRENT: 424/682; 514/251, 514/440, 514/474, 514/553, 514/561, 514/592, 514/635, 514/642

## ABSTRACT:

The compositions and dosage forms of the invention are clinically useful as methods for increasing the effectiveness, efficiency and safety of biguanides (metformin) and/or sulfonylureas in the prevention and treatment of insulin resistance and diabetes mellitus, alone or in combination, as a nutrient for humans. The carefully chosen active ingredients of the invention are designed in a modular fashion to prevent and rectify adverse events associated with insulin resistance syndrome and diabetes mellitus, and with the clinical use of biguanides (metformin) and/or the sulfonylureas. These modules are: (1) Mitochondrial Metabolic Group, (2) Plasma and Mitochondrial Membrane Integrity Group, (3) Nocturnal Group and, (4) Insulin Alternative Group. When used in concert with a biguanide, a sulfonylurea or with a combination of both, the invention will broaden the clinical usefulness of these drugs. The invention will

retard the progression of insulin resistance to type 2 diabetes, and reduce the serious microvascular and macrovascular complications commonly associated with insulin resistance syndrome and diabetes mellitus.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
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☐ 8. Document ID: US 20020177602 A1

L2: Entry 8 of 14

File: PGPB

Nov 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020177602  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20020177602 A1

TITLE: ANTIDIABETIC FORMULATION AND METHOD

PUBLICATION-DATE: November 28, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
PIPER, BETH ANNE	HOPEWELL	NJ	US	

US-CL-CURRENT: 514/291

## ABSTRACT:

A low dose antidiabetic pharmaceutical formulation is provided, especially adapted for treating Type II diabetes in drug naive patients, which includes a combination of metformin (employed in a reduced amount (less than 800 mg metformin per day) compared to that employed in generally accepted medical practice) and at least one other antidiabetic agent such as a sulfonyl urea, for example, glyburide, which combination provides at least about substantially equivalent efficacy in treating diabetes in drug naive patients, as do antidiabetic formulations containing metformin employed in dosages prescribed in generally accepted medical practice for first line therapy in treating diabetes, but with substantially reduced side effects, such as hypoglycemia and/or gastrointestinal distress. A method for treating diabetes in drug naive human patients is also provided employing the above formulation to reduce insulin resistance and/or post-prandial glucose excursion and/or hemoglobin 1Ac, and/or increase post-prandial insulin, thereby treating the diabetes.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
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☐ 9. Document ID: US 20020037928 A1

L2: Entry 9 of 14

File: PGPB

Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037928  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20020037928 A1

TITLE: Combination therapeutic compositions and method of use

PUBLICATION-DATE: March 28, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Jaen, Juan C.	Burlingame	CA	US	
Chen, Jin-Long	Foster City	CA	US	

US-CL-CURRENT: 514/616; 514/534, 514/596, 514/602, 514/617

## ABSTRACT:

The present invention provides pharmaceutical compositions and methods for the treatment of diabetes mellitus using combination therapy. The compositions relate to a compound of Formula I and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, .alpha.-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of compound of Formula I with antidiabetic agent where the two components are delivered in a simultaneous manner, where the compound of Formula I is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound of Formula I.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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 10. Document ID: US 20020013268 A1

L2: Entry 10 of 14

File: PGPB

Jan 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020013268  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20020013268 A1

TITLE: Synergistic effect of a sulfonylurea and/or non-sulfonylurea Kchannel blocker, and a phosphodiesterase 3 type inhibitor

PUBLICATION-DATE: January 31, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fryburg, David A.	East Lyme	CT	US	
Parker, Janice C.	Ledyard	CT	US	

US-CL-CURRENT: 514/3; 424/617, 514/369, 514/396, 514/592

## ABSTRACT:

The present invention provides methods of treating non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance, the methods comprising the step of administering to a patient having or at risk of having non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance a synergistic amount of: 1) a sulfonylurea, a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also provides kits and pharmaceutical compositions that comprise: 1) a sulfonylurea, a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also relates to kits and pharmaceutical compositions that comprise 1) a sulfonylurea, a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K<sub>sup</sub>.+ ATP channel blocker; 2) a cAMP phosphodiesterase type 3 inhibitor; and 3) an additional compound

useful for the treatment of non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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KMC

## ☒ 11. Document ID: US 6610746 B2

L2: Entry 11 of 14

File: USPT

Aug 26, 2003

DOCUMENT-IDENTIFIER: US 6610746 B2

TITLE: Synergistic effect of a sulfonylurea and/or non-sulfonylurea K+ATP channel blocker, and a phosphodiesterase 3 type inhibitor

### Brief Summary Text (4):

In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas, biguanides and thiazolidinediones, such as troglitazone, rosiglitazone or pioglitazone, as oral hypoglycemic agents, the treatment of diabetes can be improved.

### Brief Summary Text (23):

In a more preferred embodiment of the kits, the second compound is selected from LysPro insulin, GLP-1 (7-37) (insulinotropin), GLP-1 (7-36)-NH.sub.2, metformin, phenformin, buformin, midaglizole, isaglidole, deriglido, idazoxan, efaroxan, fluparoxan, linoglriride, ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone, clomoxir, etomoxir, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945, BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, benfluorex, fenfluramine, Naglivan.RTM., acipimox, WAG 994, Symlin.TM., or AC2993.

### Brief Summary Text (29):

In another preferred embodiment of the methods, kits, and pharmaceutical compositions, the sulfonylurea is glyburide, chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride, tolbutamide, acetohexamide, or tolazamide.

### Detailed Description Text (58):

Representative examples of additional agents that can be used include insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; biguanides: mefformin, phenformin, buformin; .alpha.2-antagonists and imidazolines: midaglizole, isaglidole, deriglido, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linoglriride, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; fatty acid oxidation inhibitors: clomoxir, etomoxir; a-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; .beta.-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; lipid-lowering agents: benfluorex; antiobesity agents: fenfluramine; vanadate and vanadium complexes (e.g. Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin agonists and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Any combination of agents can be administered as described above.

### Detailed Description Text (59):

Preferred compounds from the above classes include: LysPro insulin; GLP-1 (7-37) (insulinotropin); GLP-1 (7-36)-NH.sub.2 ; metformin; phenformin; buformin; midaglizole; isaglidole; deriglido; idazoxan; efaroxan; fluparoxan; linoglriride; ciglitazone; pioglitazone; englitazone; troglitazone; darglitazone; rosiglitazone; clomoxir; etomoxir; acarbose; miglitol; emiglitate; voglibose; MDL-25,637; camiglibose; MDL-73,945; BRL 35135; BRL 37344; Ro 16-8714; ICI D7114; CL 316,243; benfluorex; fenfluramine; Naglivan.RTM.; acipimox; WAG 994; Symlin.TM.; or AC2993.

Detailed Description Text (93):

A response surface was constructed from the combined data. From the response surface, a contour line corresponding to 95% of the maximum response level due to glyburide alone was obtained. This contour line is shown in FIG. 1. The contour line represents all the combinations of the two drugs that produce this fixed amount of response based on the data from the experiments. The plot in FIG. 1 is called an isobologram. Isobolograms are used in the study of synergism and are well known to those skilled in the art. If only an additive effect exists, the contour line would be a straight line connecting points C and D. Synergism exists if the actual contour is below the straight line.

Detailed Description Text (95):

The points C and D represent the equivalent concentrations for glyburide and milrinone, respectively. If we define C and D as one unit for glyburide and milrinone, respectively, then the dose reduction factor  $r$  represents the fraction of the combined drugs needed to achieve the same level of response achieved by one unit of either drug individually. So if  $r$  is smaller than 1, then synergism exists. The smaller the  $r$ , the stronger the synergistic effect. It is possible to mathematically determine the ratio that produced the biggest synergistic effect and the dose reduction factor  $r$  associated with the ratio. We found that the ratio is glyburide/milrinone=2.4, and the corresponding dose reduction factor  $r$  is 0.259. The implication is that with this ratio of the two drugs, only 0.259 of one unit of the combined amount of glyburide and milrinone is needed to produce the same amount of response corresponding to one unit of either glyburide or milrinone alone. FIG. 1 shows that for a wide range of ratios synergism exists.

## CLAIMS:

3. The method of claim 1 wherein the sulfonylurea is glyburide, chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride, tolbutamide, acetohexamide, or tolazamide.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 12. Document ID: US 6586438 B2

L2: Entry 12 of 14

File: USPT

Jul 1, 2003

DOCUMENT-IDENTIFIER: US 6586438 B2

TITLE: Antidiabetic formulation and method

Abstract Text (1):

A low dose antidiabetic pharmaceutical formulation is provided, especially adapted for treating Type II diabetes in drug naive patients, which includes a combination of metformin (employed in a reduced amount (less than 800 mg metformin per day) compared to that employed in generally accepted medical practice) and at least one other antidiabetic agent such as a sulfonyl urea, for example, glyburide, which combination provides at least about substantially equivalent efficacy in treating diabetes in drug naive patients, as do antidiabetic formulations containing metformin employed in dosages prescribed in generally accepted medical practice for first line therapy in treating diabetes, but with substantially reduced side effects, such as hypoglycemia and/or gastrointestinal distress. A method for treating diabetes in drug naive human patients is also provided employing the above formulation to reduce insulin resistance and/or post-prandial glucose excursion and/or hemoglobin 1Ac, and/or increase post-prandial insulin, thereby treating the diabetes.

Brief Summary Text (2):

The present invention relates to a low dose pharmaceutical formulation for treating type 2 diabetes in drug naive patients, which includes metformin (preferably employed in reduced amounts compared to that employed in generally accepted medical practice)

and another antidiabetic agent such as a sulfonyl urea, for example, glyburide, which formulation has at least substantially equivalent efficacy in treating type 2 diabetes as compared to prior art antidiabetic formulations containing metformin, but with substantially reduced side effects, and to a method for treating diabetes employing such formulations.

Brief Summary Text (4):

The biguanide antihyperglycemic agent metformin disclosed in U.S. Pat. No. 3,174,901 is currently marketed in the U.S. in the form of its hydrochloride salt (Glucophage.RTM.), Bristol-Myers Squibb Company).

Brief Summary Text (5):

The diagnosis and management of type 2 diabetes mellitus is rapidly undergoing progressive changes. It is now widely accepted that glycemic control makes a difference. The goal of diabetes therapy today is to achieve and maintain as near normal glycemia as possible to prevent the long-term microvascular and macrovascular complications of an elevated blood glucose. The diagnosis of diabetes has undergone significant changes as evidenced by the new ADA diagnostic and classification guidelines. Oral therapeutic options for the treatment of type 2 diabetes mellitus, until recently, have been severely limited. Prior to 1995, sulfonyl ureas had been the mainstay of oral diabetes agents in the United States. Sulfonyl ureas target one mechanism of hyperglycemia by augmenting insulin secretion from the beta cell. Since 1995, three new classes of agents have been added to the anti-diabetes armamentarium for the management of hyperglycemia. Metformin, a biguanide, targets additional mechanisms of hyperglycemia by inhibiting hepatic glucose production and enhancing peripheral glucose uptake and thereby reduce insulin resistance; thiazolidinediones such as troglitazone, rosiglitazone and pioglitazone decrease peripheral insulin resistance; and alpha-glucosidase inhibitors such as acarbose and miglitol help control postprandial glucose excursion by delaying absorption of dietary carbohydrate. These agents are all indicated as monotherapy and some are indicated for use in combination therapy, generally, after monotherapy has been found to be inadequate.

Brief Summary Text (6):

In 1995, metformin was added to sulfonyl urea therapy in patients who had not achieved glycemic control with sulfonyl urea monotherapy and the two agents were found to have a remarkable effect on glycemic control or lowering of hemoglobin-A1c. The different mechanisms of action in targeting hyperglycemia are complimentary and make combination use attractive and a rational course of action. Prescription data reveals approximately 60% of metformin use is in combination with a sulfonyl urea.

Brief Summary Text (7):

Examples of combinations of metformin and the sulfonyl urea glyburide (also referred to as glibenclamide) are disclosed in the following references. (1) WO 97/17975 published May 22, 1997, (Barelli et al, Istituto Gentili S.P.A.) (hereinafter Barelli et al) discloses a combination of glibenclamide and metformin in a 1:100 weight ratio, so as to allow a daily dosage of 15 mg glibenclamide and 1500 mg metformin, used for the onset of diabetes to the most severe cases, particular in cases of secondary failure to a combination of glibenclamide-metformin HCl in a weight ratio higher than 1:100. (2) Vigneri et al, Treatment of NIDDM Patients with Secondary Failure to Glyburide: Comparison of the Addition of Either Metformin or Bed-Time NPH Insulin to Glyburide, *Diabete & Metabolisme*, 1991, 17, 232-234, disclose use of a combination of 1.5 g/day metformin and 15 mg/day glyburide to treat NIDDM patients with secondary failure to 15 mg/day glyburide. (3) Higginbotham et al, Double-Blind Trial of Metformin in the Therapy of Non-Ketotic Diabetes, *The Medical Journal of Australia*, Aug. 11, 1979, 154-156, discloses treatment of diabetic patients, who were already receiving from 10 mg to 20 mg per day of glibenclamide, with 500 mg metformin twice a day. Higginbotham et al conclude "that in selected diabetics whose condition is inadequately controlled with sulphonylurea therapy, significant improvement in diabetic control can be obtained by the addition of metformin in a low dose of 500 mg twice a day." (4) U.S. application Ser. No. 09/353,141, filed Jul. 14, 1999 (based on European application No. 98401781.4, filed Jul. 15, 1998) discloses formulations containing metformin and glyburide where the glyburide is of a particular particle size as described hereinafter.

Brief Summary Text (8):

References which disclose combinations of metformin and glipizide include the following: (1) Combination of glipizide/metformin treatment reduces low density lipoprotein binding to arterial proteoglycans in DDDM, Edwards et al, *Diabetes*, (46, Suppl. 1, 45A, 1997). (2) Combination of glipizide/metformin normalizes glucose and improves insulin sensitivity in hyperinsulinemia moderately well controlled. Cefalu et

al, Diabetes, (45, Suppl. 2, 201A, 1996). (3) Effects of combination of glipizide/metformin treatment on oxidizability of LDL in NIDDM, Crouse et al, Circulation, (94, No. 8, Suppl., 1508, 1996). (4) Insulin sensitivity is improved after glipizide monotherapy and combination with metformin, Cefalu et al, Diabetologia, (39, Suppl. 1, A231, 1996). (5) Combined Metformin--Sulfonyl urea Treatment of Patients with NIDDM in Fair to Poor Glycemic Control, Reaven et al, J. Clin. Endocrinol. Metab. (74, No. 5, 1020-26, 1992). (6) Combination of Glipizide/Metformin Treatment in NIDDM, Hollenbeck et al, Diabetes, (39, Suppl. 1, 108A, 1990). (7) Oral Antidiabetic Combination Therapy with Sulfonyl ureas and Metformin, Haupt et al, Med. Welt. (40, No. 5, 118-23, 1989). (8) Variation of the lipemic pattern in diabetic subjects after treatment with a combination of glipizide and metformin, Ferlito et al, PROGR. MED. (Roma) 31/6 (289-301) 1975. (9) Results with a combination of glipizide and dimethylbiguanide in 40 cases of diabetes, Parodi et al, GAZZ. MED. ITAL. 132/5 (226-235) 1973.

#### Brief Summary Text (9):

Other combinations of metformin and another antidiabetic agent are disclosed in the following references. (1) U.S. Pat. No. 5,631,224 to Efendic et al discloses a combination of metformin with GLP-1(7-36) amide or GLP-1(7-37) or a fragment thereof. (2) WO 98/57634 (SKB) discloses a method for treating diabetes employing a combination of a thiazolidenedione and metformin. The thiazolidenedione may be troglitazone, ciglitazone, pioglitazone or englitazone, and may be employed in dosages of 2 to 12 mg per day while the metformin may be employed in daily dosages "of up to 3000 mg per day, in unit doses of 500 mg (for example, 2 to 3 times per day) or 850 mg (2 times per day), one example of a dosage for metformin is 500 mg building to 5 times per day." (3) EP 0749751A2 (Takeda) discloses a combination of a thiazolidenedione insulin sensitivity enhancer (such as pioglitazone) and metformin.

#### Brief Summary Text (10):

None of the above references suggests employing diabetic combinations containing metformin for first line treatment of drug naive patients.

#### Brief Summary Text (11):

Several fixed combinations of metformin and glyburide (glibenclamide) are presently being marketed outside the U.S. These include (1) combinations of 400 mg metformin/2.5 mg glibenclamide (Boehringer's Bi-Euglucon in Argentina, and Bi-Euglicon M in Italy; Guidotti/Menarini's Glibomet in the Dominican Republic and Italy; HMR's Normell in Greece and Hoechst's Suguan-M in Italy; Sun Pharma's Glucored in India; Monsanto's (Searle's) Benclamet in India; Guidotti's Globate in Liban; Berlin Chemie/Menarini's Glibomet in the Slovak Rep., and Roche's Bi-Euglucon in Uruguay); (2) combinations of 500 mg metformin/5 mg glibenclamide (Sun Pharma's Glucored in India; Monsanto's (Searle's) Benclamet in India, USV's Duotrol in India; and Lakeside's (Roche) Bi-Euglucon M5 in Mexico); (3) combinations of 500 mg metformin/2.5 mg glibenclamide (Molteni's Glucomide in Italy, Lakeside's (Roche) Bi-Euglucon M in Mexico and Szabo's Dublex in Uruguay); and (4) 1 g metformin/5 mg glibenclamide (Silanes Sil-Norboral in Mexico).

#### Brief Summary Text (12):

The labelling for Glucophage.RTM. (Bristol-Myers Squibb's metformin), in the Physicians' Desk Reference 1999, under "Indications and Use", indicates that Glucophage may be used concomitantly with a sulfonylurea. It is further indicated under "Dosage and Administration" "Concomitant Glucophage and Oral Sulfonylurea Therapy" that "If patients have not responded to four weeks of the maximum dose of Glucophage monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing Glucophage at the maximum dose . . . With concomitant Glucophage and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the maximum effective dose of each drug to achieve this goal." The recommended dosing schedule for Glucophage is a starting dose of 500 mg twice a day or 850 mg once a day with dosage increases in increments of 500 mg weekly or 850 mg every 2 weeks up to a total of 2000 mg per day.

#### Brief Summary Text (13):

Package inserts for Bi-Euglucon M and Suguan M in Italy (400 mg metformin/2.5 mg glibenclamide) indicate that these drug combinations are used in cases of primary or secondary resistance to sulfonyl ureas [that is as second or third line therapy] and that a dosage of 1/2 tablet per day increasing 1/2 tablet at a time according to glycemic variations up to 4 tablets per day are employed.

Brief Summary Text (14):

Package inserts for Glibomet (400 mg metformin/2.5 mg glibenclamide) and Glucoside (500 mg metformin/2.5 mg glibenclamide) in Italy indicate that these drug combinations are used for treating type 2 diabetes which is non-controllable or cannot be controlled with only diet or with diet and sulfonyl urea [that is as first line therapy of second line therapy].

Brief Summary Text (15):

The package insert for Glibomet in Italy indicates a daily dosage of 2 tablets, that is 800 mg metformin and 5 mg glibenclamide, up to 2 grams metformin. The package insert for Glucoside in Italy indicates a daily dosage of 2 capsules, that is 1000 mg metformin up to 2 grams metformin, and 5 mg glibenclamide.

Brief Summary Text (17):

In accordance with the present invention, a low dose pharmaceutical formulation is provided which includes a combination of metformin and at least one other antidiabetic agent, which preferably is glyburide, which combination provides at least substantially equivalent efficacy in treating diabetes in drug naive patients (in first line therapy) as do combinations of metformin and the other antidiabetic agent employed in substantially higher dosages as prescribed in generally accepted medical practice for first line therapy in treating diabetes. However, use of the low dose pharmaceutical formulation of the invention results in substantially reduced side effects as compared to the same combination employed in the higher doses as generally prescribed.

Brief Summary Text (18):

It is to be understood that the low dose formulation of the invention will include a "low dose" of at least one of the active antidiabetes drug components, that is a lower dosage than the dosage for such drug prescribed in generally accepted medical practice in first line therapy of treating diabetes. Thus, the above low dose pharmaceutical formulation will include a low dose of metformin as defined hereinafter, or a low dose of other antidiabetic agent as defined hereinafter, or a low dose of each of metformin and other antidiabetic agent as defined hereinafter.

Brief Summary Text (19):

In accordance with the present invention, efficacy in first line therapy in treating diabetes in drug naive patients is achieved employing the low dose pharmaceutical formulation of the invention wherein the daily dosage of the metformin may be employed in a daily dosage prescribed in generally accepted medical practice for first line therapy in treating diabetes, and is preferably within the range which comprises a starting daily dosage as low as about one-fifth of the starting daily dosage of metformin employed in generally accepted medical practice for first line therapy for treating diabetes, up to a daily maintenance dosage of about two-thirds of the daily maintenance dosage of metformin employed in generally accepted medical practice for first line therapy for treating diabetes.

Brief Summary Text (20):

The low dose pharmaceutical formulation of the invention will more preferably contain metformin where the daily dosage of the metformin is within the range which comprises a starting daily dosage as low as about 25% up to about 60% of the starting daily dosage of metformin employed in generally accepted medical practice for first line therapy for treating diabetes, up to a daily maintenance dosage of from about 40 to about 60% of the maintenance dosage employed in generally accepted medical practice for first line therapy for treating diabetes.

Brief Summary Text (21):

Thus, in effect, the low dose pharmaceutical formulation of the invention will be employed in first line therapy in a daily dosage to provide less than about 800 mg metformin per day, preferably no more than about 750 mg metformin per day, more preferably no more than about 600 mg metformin per day, and a minimum (starting dosage) of about 160 to about 225 mg per day, in single or divided doses of one to four tablets daily.

Brief Summary Text (25):

The term "low dose combination", "low dose formulation" or "low dose pharmaceutical formulation" as employed herein, in a preferred formulation of the invention, refers to a formulation which includes metformin in a starting daily dosage of as low as about one-fifth the starting daily dosage of metformin prescribed in generally accepted medical practice for first line therapy in treating diabetes up to about two-thirds the maintenance daily dosage of metformin prescribed in generally accepted medical practice

for first line therapy in treating diabetes. The above daily dosage of metformin includes starting daily dosages of metformin (for example as low as 160 mg) and dosages of metformin titrated up to a maximum maintenance dosage of less than about 800 mg metformin per day, preferably less than about 750 mg per day; and other antidiabetic agent employed in amounts set out herein.

Brief Summary Text (26):

Until now, combinations of metformin and another antidiabetic drug, for example, a sulfonyl urea, such as glyburide, have normally been used with few exceptions, as second line therapy in treating type 2 diabetes. Generally accepted medical practice daily dosages for such second line therapy employing fixed combinations of metformin and glyburide range from 3 to 4 tablets containing 400 to 500 mg metformin and 2 to 2.5 mg glyburide, or about 1200 to 2000 mg metformin and 6 to 10 mg glyburide, daily.

Brief Summary Text (27):

As indicated above with respect to Glibomet and Glucoside (fixed combinations of metformin and glyburide) marketed in Italy, these combinations may be employed as first line therapy (drug naive patients) in a daily dosage of 800 to 1000 mg up to 2 grams metformin and 5 mg glibenclamide (glyburide). This daily dosage is referred to herein as "dosages prescribed in generally accepted medical practice for first line therapy in treating diabetes" or as dosages of "prior art combinations" or "prior art daily dosages."

Brief Summary Text (29):

As indicated above with respect to Boehringer's Bi-Euglucon M and Hoechst's Suguan M (fixed combinations of metformin and glibenclamide) marketed in Italy, these combinations are employed as second line therapy in a daily dosage starting at 1/2 tablet, that is, 200 mg metformin and 1.25 mg glibenclamide. The initial or starting low doses are employed to determine if the patient can tolerate the drugs and these doses are gradually titrated upwardly 1/2 tablet at a time up to 4 tablets per day until an efficacious dosage is achieved. The initial or starting daily dosage of 1/2 tablet or 200 mg metformin and 1.25 mg glibenclamide is not considered by Boehringer and Hoechst and physicians prescribing these drugs as "dosages as prescribed in generally accepted medical practice for treating diabetes."

Brief Summary Text (30):

Surprisingly, it has been found that use of the combination of metformin and glyburide in accordance with the present invention affords the following benefits. The low dose metformin is an insulin sensitizer and decreases insulin resistance at the liver, muscle and pancreas. The low dose metformin-glyburide combination acts on the pancreas as a glucose sensitizer; it decreases glucose toxicity at the pancreas and improves function of the pancreas.

Brief Summary Text (31):

In addition, in accordance with the present invention, a method is provided for treating diabetes, especially type 2 diabetes, in a drug naive human patient, which includes the step of administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose pharmaceutical formulation of the invention which includes a combination of metformin and at least one other antidiabetic agent (preferably glyburide), in dosages as described herein, which combination provides at least substantially equivalent efficacy in treating diabetes in drug naive patients as do combinations of metformin and said other antidiabetic agent employed in dosages prescribed in generally accepted medical practice for first line therapy treating diabetes, but with substantially reduced side effects.

Brief Summary Text (32):

In addition, in accordance with the present invention, a method is provided for decreasing fasting plasma glucose, decreasing insulin resistance, decreasing hemoglobin Alc, increasing post-prandial insulin and/or decreasing post-prandial glucose excursion in a human diabetic patient, which includes the step of administering to a human patient the low dose pharmaceutical formulation of the invention which includes a combination of metformin/other antidiabetic agent, preferably glyburide. It is preferred that the low dose pharmaceutical formulation be administered as first line therapy and that the human patient be a drug naive patient.

Brief Summary Text (33):

In carrying out the method of the invention employing the preferred low dose pharmaceutical formulation of the invention containing metformin and glyburide, to treat drug naive patients for diabetes, it has been found that the efficacy in treating

drug naive patients is at least substantially equivalent and incidence of side effects (gastrointestinal side effects and hypoglycemia) is surprisingly significantly and substantially reduced as compared to patients on prior art daily dosages of metformin and glyburide (that is in dosages prescribed in generally accepted medical practice for treating diabetes). Thus, while efficacy in treating drug naive patients as measured by decrease in hemoglobin A.sub.1c from baseline over time, decrease in fasting plasma glucose (FPG), increase in post-prandial insulin levels, and decrease in post-prandial glucose (PPG) excursion, are essentially substantially equivalent in the above-described patients when employing the low dose pharmaceutical formulation of the invention and the prior art daily dosages or prior art combinations, incidence of hypoglycemia in drug naive patients treated with prior art daily dosages is more than 3 times greater than in patients treated with the low dose pharmaceutical formulation of the invention, and incidence of gastrointestinal side effects in drug naive patients treated with prior art daily dosages is more than 20% greater than patients treated with the low dose pharmaceutical formulation of the invention.

Brief Summary Text (34):

Preferred daily dosages of a combination of metformin and glyburide will be in the range from about 175 to about 600 mg metformin, more preferably from about 200 to about 500 mg metformin, still more preferably from about 250 to about 400 mg metformin, and from about 0.5 to about 4.5 mg glyburide, preferably from about 0.625 to about 3.75 mg glyburide, and more preferably from about 1 to about 1.5 mg glyburide.

Brief Summary Text (37):

The term "metformin" as employed herein refers to metformin or a pharmaceutically acceptable salt thereof such as the hydrochloride salt, the metformin (2:1) fumarate salt, and the metformin (2:1) succinate salt as disclosed in U.S. application Ser. No. 09/262,526 filed Mar. 4, 1999, the hydrobromide salt, the p-chlorophenoxy acetate or the embonate, and other known metformin salts of mono and dibasic carboxylic acids including those disclosed in U.S. Pat. No. 3,174,901, all of which salts are collectively referred to as metformin. It is preferred that the metformin employed herein be the metformin hydrochloride salt, namely, that marketed as Glucophage.RTM. (trademark of Bristol-Myers Squibb Company).

Brief Summary Text (41):

The low dose pharmaceutical formulation of the invention will contain metformin used in combination with another antidiabetic agent (also referred to herein as "another antihyperglycemic agent") which may be administered orally in the same dosage form or in separate oral dosage forms or by injection.

Brief Summary Text (43):

It is believed that the use of metformin in combination with another antidiabetic agent in accordance with the present invention produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

Brief Summary Text (44):

The other antidiabetic agent will preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Pat. No. 4,379,785), glipiride, glipizide, gliclazide or chlorpropamide, and/or other known sulfonyl ureas or other antihyperglycemic agents which act on the ATP-dependent channel of the .beta.-cells, with glyburide being most preferred. The sulfonyl urea may be administered in the same oral dosage form with metformin or a separate oral dosage form.

Brief Summary Text (45):

Metformin will be employed in a weight ratio to the sulfonyl urea in the range from about 1000:1 to about 10:1, preferably from about 400:1 to about 100:1, more preferably from about 250:1 to about 150:1, and optimally about 200:1.

Brief Summary Text (46):

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Pat. No. 4,904,769), vaglibose, miglitol (disclosed in U.S. Pat. No. 4,639,436), which may be administered in a separate oral dosage form or the same dosage form with metformin.

Brief Summary Text (47):

Metformin will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

Brief Summary Text (48):

The other antidiabetic agent may be a meglitinide, for example, repaglinide (Prondin.RTM., NovoNordisk) or nataglinide (Starlex.RTM., Novartis), which may be administered in a separate oral dosage form or the same oral dosage form with metformin.

Brief Summary Text (49):

Metformin will be employed in a weight ratio to the meglitinide within the range of from about 0.01 to about 500:1, preferably from about 0.5:1 to about 300:1.

Brief Summary Text (50):

Metformin may be employed in combination with a thiazolidinedione oral antidiabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Labert's Rezulin.RTM., disclosed in U.S. Pat. No. 4,572,912), rosiglitazone (SKB-Avandia.RTM.), pioglitazone (Takeda-Lilly-Actos.RTM.), Mitsubishi's MCC-555 (disclosed in U.S. Pat. No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer), which may be administered in a separate oral dosage form or the same oral dosage form with metformin.

Brief Summary Text (51):

Metformin will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

Brief Summary Text (52):

The thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with metformin.

Brief Summary Text (54):

Metformin will be employed in a weight ratio to the  $\alpha$ 2 inhibitor in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 2:1. The  $\alpha$ 2 inhibitor and metformin may be incorporated in the same or separate dosage forms.

Brief Summary Text (55):

Metformin may also be employed in combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Pat. No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be administered via injection, or by transdermal or buccal devices.

Brief Summary Text (56):

Where present, the sulfonil urea, such as glyburide, glimepiride, glipyrider, glipizide, chlorpropamide or gliclazide, the thiazolidinedione, such as troglitazone, rosiglitazone or pioglitazone, the glucosidase inhibitor acarbose or miglitol, the meglitinide such as repaglinide or nataglinide, or insulin may be employed in formulations as described above and in formulations, amounts and dosing as indicated in the Physicians' Desk Reference.

Brief Summary Text (58):

Metformin may be employed in combination with another antidiabetic agent which may be a PPAR .alpha./.gamma. dual agonist such as an N-benzylidioxothiazolidylbenzamide derivative such as disclosed in WO 96/38428 such as 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-[4-(trifluoromethyl)benzyl ]benzamide (KRP-297), WO 98/05531 (Ligand Pharmaceuticals, Inc.) which discloses 2-(4-[2,4-difluorophenyl]-1-heptylureido)ethyl]phenoxy)-2methylbutyric acid, and WO 97/25042 and WO96/04260 (SKB) which disclose benzoxazole and pyridine derivatives of the structure ##STR1##

Brief Summary Text (60):

Metformin will be employed in a weight ratio to the PPAR .alpha./.gamma. dual agonist within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

Brief Summary Text (61):

Where metformin is employed in combination with the PPAR .alpha./.gamma. dual agonist, the combination may be employed in an oral dosage form such as a tablet or capsule as will be apparent to one skilled in the art.

Brief Summary Text (62):

Preferred are low dose combinations of metformin and glyburide and optionally an insulin sensitizer such as a glitazone, for example, rosiglitazone, pioglitazone or troglitazone.

Brief Summary Text (63):

In carrying out the present invention, a low dose pharmaceutical formulation or composition will be employed containing metformin and at least one other antidiabetic agent in association with a pharmaceutical vehicle or diluent. The low dose pharmaceutical formulation can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The low dose pharmaceutical formulation of the invention can be administered to mammalian species including humans, monkeys, dogs, etc., by an oral route, for example, in the form of tablets, capsules, granules or powders, or it can be administered by a parenteral route in the form of injectable preparations. The dose for drug naive patients is as described above, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

Brief Summary Text (66):

The combination of the metformin or salt thereof and the other antidiabetic agent may be formulated separately or, where possible, in a single formulation employing conventional formulation procedures.

Brief Summary Text (74):

Where the low dose pharmaceutical formulation of the invention includes a combination of metformin and glyburide, the formulation will be administered so as to provide from about 55 to about 500 mg metformin one to four times daily, with a minimum of about 160 mg metformin daily and a maximum of less than about 800 mg, preferably up to about 750 mg metformin daily. The glyburide will preferably be administered in an amount from about 0.5 to about 3.75 mg one to four times daily, with a maximum of up to about 4.5 mg daily.

Brief Summary Text (75):

The preferred low dose pharmaceutical formulation of the invention is comprised of metformin and glyburide and is employed as initial therapy that is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Brief Summary Text (77):

Dosage of the preferred metformin-glyburide combination of the invention must be individualized on the basis of both effectiveness and tolerance. It is preferably given with meals and should be started at a low dose, with gradual dose escalation. Ideally, the response to therapy should be evaluated using HbA.sub.1c (glycosylated hemoglobin) which is a better indicator of long-term glycemic control than FPG alone. The therapeutic goal in all patients with type 2 diabetes mellitus should be to improve glycemic control, including FPG, postprandial glucose and HbA.sub.1c levels, to normal or as near normal as possible. Patients should be titrated to achieve the ADA goal of HbA.sub.1c >7% following the dosing recommendations up to the maximum recommended dose. (ADA. Diabetes Care 21 [Suppl. 1]:S23-S32, 1998).

Brief Summary Text (78):

As initial therapy, the preferred starting dose of the metformin-glyburide combination of the invention is 250/1.25 mg once a day, given with a meal. For patients with a baseline HbA.sub.1c >9% or a fasting glucose >200 mg/dL, a recommended starting dose of 250/1.25 mg twice daily with the morning and evening meal may be preferred. Dosage increases should preferably be made in increments of 250/1.25 mg, every 2 weeks, up to the minimum effective dose necessary to achieve adequate glycemic control. For those patients requiring additional glycemic control, the 250 mg/1.25 mg dosage may be switched to 500/2.5 mg. However, as indicated, the preferred maximum daily dosage for metformin is 600 to 750 mg and the preferred maximum daily dosage for glyburide is 3.75 mg.

Brief Summary Text (79):

The low dose pharmaceutical formulation containing the metformin-glyburide combination, in accordance with the present invention, will preferably be formulated according to the teachings disclosed in U.S. application Ser. No. 09/353,141, filed Jul. 14, 1999, which claims priority from European application No. 98401781.4 filed Jul. 15, 1998, which U.S. application is incorporated herein by reference.

Brief Summary Text (80):

The preferred low dose metformin-glyburide formulation is set out below.

Brief Summary Text (81):

The especially preferred low dose metformin-glyburide formulations are as follows:

Brief Summary Text (82):

The low dose pharmaceutical formulation of the invention in the form of a solid oral form such as a tablet, will preferably contain a combination of metformin and glyburide in which the size of the glyburide is such that at most 10% of the particles are less than 2 .mu.m and at most 10% of the particles are greater than 60 .mu.m. Preferably, the size of the glyburide is such that at most 10 of the particles are less than 3 .mu.m and at most 10% of the particles are greater than 40 .mu.m. This specific size range of glyburide may be obtained by sieving or air jet milling.

Brief Summary Text (83):

In a second embodiment, the low dose solid oral dosage form of the invention will contain a combination of metformin and glyburide in which the size of glyburide is such that at most 25% of the particles are less than 11 .mu.m and at most 25% of the particles are greater than 46 .mu.m.

Brief Summary Text (85):

Most preferred are a combination of metformin and glyburide, where the glyburide has a particle size distribution of about 25% undersize value not more than 6 .mu.m, about 50% undersize value 7 to 10 .mu.m and about 75% undersize value not more than 23 .mu.m.

Brief Summary Text (86):

The low dose pharmaceutical formulation of the invention in the form of a tablet may be obtained by a process which includes the steps of a) forming granules by wet granulation of a mixture of metformin and glyburide b) blending the granules with a tableting aid and diluent, and c) tableting the blend thus obtained into tablets.

Brief Summary Paragraph Table (1):

Amount of ingredient, mg per tablet Product identity 250/1.25 Ingredient Metformin hydrochloride 250.0 Glyburide 1.25 Croscarmellose sodium 3.0-15.0 Microcrystalline cellulose 15.0-60.0 Polyvinyl pyrrolidone 3.0-18.0 Magnesium stearate 0.3-7.5 Film coat\* 4.5-12.0 \*a commercially available film coat composition is used, such as Opadry (Colorcon, UK).

Brief Summary Paragraph Table (2):

Amount of ingredient, mg per tablet Product identity 250/1.25 Ingredient Metformin hydrochloride 250.0 Glyburide 1.25 Croscarmellose sodium 7.0 Microcrystalline cellulose 28.25 Polyvinyl pyrrolidone 10.0 Magnesium stearate 0.6-6.0 Film coat\* 4.5-12.0 \*a commercially available film coat composition is used, such as Opadry (Colorcon, UK).

Drawing Description Text (2):

FIGS. 1 and 2 are bar graphs which depict change in hemoglobin A1c (HbA1c) by number of tablets of fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Drawing Description Text (3):

FIGS. 3, 4 and 5 are bar graphs which depict change in HbA1c over time of fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Drawing Description Text (4):

FIG. 6 is a bar graph which depicts change in fasting plasma glucose (FPG) by number of tablets of fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Drawing Description Text (5):

FIG. 7 is a bar graph which depicts baseline and post-prandial insulin levels of fixed combinations of metformin/glyburide in first line therapy versus monotherapy with glyburide and metformin.

Drawing Description Text (6):

FIGS. 8A and 8B are bar graphs which depict change in PPG excursion at baseline and

after 20 weeks of fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Drawing Description Text (7):

FIG. 9 is a bar graph which depicts hypoglycemic symptoms in subjects on fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Drawing Description Text (8):

FIG. 10 is a bar graph which depicts frequency of gastrointestinal adverse effects in subjects on fixed combinations of metformin/glyburide used in first line therapy versus monotherapy with each of glyburide and metformin.

Detailed Description Text (3):

Tablets containing metformin/glyburide combinations were prepared as described below.

Detailed Description Text (4):

The metformin hydrochloride-glyburide tablet products, 250 mg/1.25 mg and 500 mg/2.5 mg, were compressed from the same granulation. The lower strength tablet was compressed at half the weight of the metformin hydrochloride-glyburide 500 mg/2.5 mg tablet. Tablets manufactured for clinical use were film-coated with a hydroxypropylmethylcellulose (HPMC) film coat. The film coat was non-functional and was applied for aesthetic purposes. The film coat applied to the clinical product was clear.

Detailed Description Text (6):

Croscarmellose sodium and glyburide were dispersed together followed by blending with the metformin hydrochloride/magnesium stearate (99.5%:0.5% w/w) in a high shear mixer. The resultant dry mix was granulated in a high shear mixer with an aqueous povidone solution and dried in a fluid bed dryer at approximately 60.degree. C. to achieve a specified moisture content, determined by loss on drying. The dried granulation was reduced with a screening mill and mixed with the microcrystalline cellulose using a tumble mixer. Magnesium stearate was incorporated as a lubricant using a tumble mixer to produce the final compression blend.

Detailed Description Text (10):

The proposed particle size specification included the three cumulative size criteria described above with a range for acceptable mass median particle size (50% undersize) and an upper limit for the lower quartile (25% undersize), and the upper quartile (75% undersize). The particle size specification established for glyburide had been based on the particle size of glyburide used in bioavailability studies, the experience of various clinical lots, the closely matching nature of the size distributions of commercially produced glyburide and the particle size method precision. The particle size criteria described below assured reproducibility of glyburide dissolution and bioavailability from metformin hydrochloride-glyburide tablets. 25% undersize value not more than 6 .mu.m 50% undersize value 7-10 .mu.m 75% undersize value not more than 23 .mu.m

Detailed Description Text (14):

The following study was conducted to compare glycemic control of 2 dosage strengths of a fixed combination metformin/glyburide product (described in Examples 1 and 2) versus placebo in drug naive patients with type 2 diabetes mellitus who have had inadequate glycemic control with diet and exercise. The dosage strengths of fixed combination product evaluated included metformin 250 mg with glyburide 1.25 mg, and metformin 500 mg with glyburide 2.5 mg. Glycemic control was assessed using Hemoglobin Alc (HbA.sub.1c), the gold-standard measure of long-term glycemic control. Mean change from baseline in HbA.sub.1c following a 20 week treatment period (4 weeks stable once daily dose, 4 week titration and 12 weeks stable dose) were compared. The treatment phase continued for an additional 12 weeks to assess durability of efficacy.

Detailed Description Text (15):

Contribution of the individual components of the fixed combination product were assessed by comparison of short term glycemic parameters of the combination product and monotherapy arms after 4 weeks of stable once daily dosing. Glycemic control was achieved with similar incidence of hypoglycemia with the fixed dose combinations as compared with sulfonyl urea alone or trends towards decreased gastrointestinal side effects as compared with metformin alone. Glycemic control was achieved with trends toward decreased adverse events as compared with either agent alone. Trends in hypoglycemia, gastrointestinal symptoms and lactate levels were assessed.

Detailed Description Text (25):

Metformin and sulfonyl ureas, such as glyburide, are a known and effective combination in the treatment of type 2 diabetes mellitus. The two drugs have demonstrated a synergistic effect on glucose lowering when used in combination. Either drug can be used alone as first line monotherapy. They may also be used in combination with each other if monotherapy of either is inadequate. No data currently exists on the use of low dose combination therapy for first line use.

Detailed Description Text (27):

This randomized double-blind, placebo-controlled study in subjects with type 2 diabetes mellitus who have inadequate glycemic control on diet and exercise tested the following hypotheses: 1. Administration of a fixed dose metformin/glyburide combination product for 20 weeks (4 weeks stable once daily dosing in Period B and 16 weeks of treatment in Period C) in subjects with type 2 diabetes mellitus who have inadequate glycemic control on diet and exercise will produce significant reductions in HbA.sub.1c compared to placebo. 2. Administration of a fixed dose metformin/glyburide combination product for 32 weeks in subjects with type 2 diabetes mellitus who have inadequate glycemic control on diet and exercise will be well tolerated.

Detailed Description Text (30):

To compare, after 20 weeks of oral administration, the effect of 2 dosage strengths (Examples 1 and 2) of a fixed combination metformin/glyburide tablet that has been titrated for glycemic control on the reduction in HbA.sub.1c level versus placebo.

Detailed Description Text (31):

(2) Secondary (Included the Following) 1. To assess safety and tolerability among treatment arms after 20 and 32 weeks of randomized therapy. Glycemic control may be achieved with a similar incidence in hypoglycemia with the fixed dose combinations as compared with sulfonyl urea alone or decreased gastrointestinal side effects as compared with metformin alone. 2. To assess after 20 weeks and assess after 32 weeks, the proportion of subjects with a therapeutic response in glycemic control of oral administration of each metformin/glyburide combination regimen when compared to the therapeutic response achieved with metformin monotherapy, glyburide monotherapy and placebo regimens. Therapeutic plasma glucose response will be defined as a FPG<126 mg/dL (based on current ADA guidelines for FPG). Therapeutic response for HbA.sub.1c will be defined as HbA.sub.1c <7%. 3. To assess after 20 weeks and assess after 32 weeks, the reductions in fasting glucose and 2-hour postprandial glucose and insulin levels following the oral administration of each fixed combination metformin/glyburide regimen with the reduction in fasting glucose and 2-hour postprandial glucose and insulin level achieved with metformin monotherapy, glyburide monotherapy and placebo. 4. To assess the durability of reductions in HbA.sub.1c levels after 32 weeks of administration of fixed combination metformin/glyburide product. 5. To assess long-term safety and efficacy of fixed combination metformin/glyburide products.

Detailed Description Text (33):

This was a multicenter, randomized, five-arm, parallel group, double-blind, placebo controlled trial of the antihyperglycemic activity of a fixed combination metformin/glyburide tablet as first line therapy in subjects with type 2 diabetes mellitus who have inadequate glycemic control (HbA.sub.1c <7%), with diet and exercise. Patients were drug naive or had no oral antihyperglycemic therapy for the 2 months prior to screening. Approximately 100 US sites enrolled up to a maximum of 800 patients with type 2 diabetes mellitus who had inadequate glycemic control defined as an HbA.sub.1c between 7-11% on diet and exercise. The minimum number of patients required to achieve the primary outcome was a total of 500 patients or 100 patients per arm. However, recruitment continued for up to 6 months to recruit up to a maximum of 150 patients per arm to provide additional safety information. The design included 3 periods as follows:

Detailed Description Text (38):

Period B began the randomized, double-blind, parallel quadruple dummy treatment phase. Eligible patients were randomized to 1 of 5 study arms which included placebo, glyburide monotherapy, metformin monotherapy, and two different dose strengths of fixed combination metformin/glyburide product (Examples 1 and 2). Subjects were maintained on once daily dosing for a 4 week period so that the contribution of the individual components of the combination product can be assessed by short term glycemic parameters.

Detailed Description Text (44):

Study drugs for this study were defined as: placebo, glyburide, metformin, metformin/glyburide 250/1.25 mg and metformin/glyburide 500/2.5 mg. For blinding purposes this study incorporated a quadruple-dummy design. Patients meeting the inclusion criterion without meeting any exclusion criterion, satisfying the Period A glycemic criteria, were eligible for enrollment into Period A.

Detailed Description Text (50):

Following completion of the single-blind lead-in phase (Period A), qualifying subjects commenced therapy in the randomized, double-blind treatment phase (Period B). At visit A15/B1 subjects were randomized to once daily dosing with breakfast of placebo, glyburide 2.5 mg, metformin 500 mg, metformin/glyburide 250/1.25 mg or metformin/glyburide 500/2.5 mg. once daily dosing remained stable for a total of 4 weeks.

Detailed Description Text (52):

Following completion of the 4 week stable once daily dose phase (Period B) subjects continued the same randomized therapy in the 28 week titration/stable dose treatment phase (Period C). Study medication was titrated at visits C1, C15 and C29. Medication was dosed with the first morning meal and with the evening meal. Potential maximal doses achieved included glyburide 10 mg, metformin 2000 mg, metformin/glyburide 1000/5 mg, metformin/glyburide 2000/10 mg. After the 4 week titration segment in Period C, subjects continued on a stable dose of study medication for the remainder of Period C.

Detailed Description Text (55):

The results obtained from the above studies indicate that the low dose metformin-glyburide (250/1.25) formulation of the invention achieved glycemic control at least essentially equivalent to the high dose metformin-glyburide (500/2.5) formulation as evidenced by (1) a therapeutic response for hemoglobin A1c, namely, a reduction in HbA1c of below 7% (from a mean baseline of 8.2%) at week 20 (FIGS. 1, 2 and 3), at weeks 20 and 32 and final visit (FIGS. 4 and 5) (2) a therapeutic response for fasting plasma glucose (FPG), namely, a reduction in FPG to less than 126 mg/dL after 20 weeks (from a baseline of about 175 mg/dL), (as shown in FIGS. 6) (3) a therapeutic response for post-prandial insulin levels, namely an increase in post-prandial insulin of 19-25 .mu.iu/mL (microinternational units/mL) (FIG. 7) (4) a therapeutic response for post-prandial glucose excursion (PPG) (that is the difference between post-prandial glucose and fast plasma glucose), namely, a decrease in post-prandial glucose excursion at week 20 of 17.7 for the 500/2.5 mg combo and 20.8 for the 250/1.25 mg combo versus 15.2 for metformin, 6.8 for glyburide. (FIGS. 8A and 8B).

Detailed Description Text (63):

While a fixed combination of metformin and glyburide is not a novel concept, and, as discussed above, different forms of it are available outside the U.S. for first and second line therapy, the use of combination therapy, low or moderate dose, as first line treatment in drug naive patients has never been studied in large controlled clinical trials. Treating to a near euglycemic target, an HbA<sub>1c</sub> <7% as recommended by the ADA, is the goal with any antihyperglycemic therapy. However, depending upon the duration of diabetes and the progression of the disease, a single agent may not provide the efficacy necessary to bring even newly diagnosed patients to their target goal. The data presented in this summary provides evidence that a low dose fixed combination metformin/glyburide product is safe and provides the efficient antihyperglycemic potency necessary to bring most drug naive patients to the ADA's recommended glycemic target.

Detailed Description Text (64):

As first line therapy, a single formulation of fixed combination metformin/glyburide in ratio of a 200:1 metformin/glyburide was evaluated using two different dose strengths, a low dose (metformin/glyburide 250/1.25 mg) and a medium dose (metformin/glyburide 500/2.5 mg). The two dose strengths of fixed combination metformin/glyburide product were compared in a double-blind study to placebo, glyburide monotherapy and metformin monotherapy. Mean final doses achieved in each treatment arm were approximately 5.3 mg of glyburide, 1307 mg of metformin, 557/2.78 mg of low dose (250/1.25 mg) metformin/glyburide fixed combination and 818/4.1 mg of medium dose (500/2.5 mg) fixed combination. When used as first line therapy, fixed combination metformin/glyburide treatment achieved statistically significant improvement in glycemic control compared to metformin, glyburide or placebo. The interim open-label treatment data confirmed the clinical utility of fixed combination therapy in a more "glycemically diverse" patient population and for a longer period of time. Safety As first line therapy use, two dose strengths of metformin/glyburide were evaluated; a low-dose (250/1.25 mg) and a medium

dose (500/2.5 mg) strength were compared with placebo, glyburide and metformin. In the double-blind phase of this study, diarrhea was the most frequently-occurring adverse effects (AE) in those subjects who were on metformin mono- or combination therapy. Importantly, however, the incidence of gastrointestinal AEs was lower in the low dose fixed combination group than in the metformin monotherapy group (as seen in FIG. 10). Discontinuations due to AEs also occurred with the lowest frequency in the low dose fixed combination group compared to any of the other active treatments. Discontinuations due to lack of glycemic control were lowest in both the fixed combination groups, and severe hypoglycemia was not observed in this study. The frequency of subjects reporting an episode of hypoglycemia was highest in the medium dose fixed combination treatment group, while the low dose group had a lower incidence than glyburide monotherapy (FIG. 9). Mild increase in lactate levels were observed in all metformin groups, but no cases of lactic acidosis were reported in this study.

Detailed Description Text (66):

In both the newly-diagnosed subjects as well as inadequately-controlled subjects, the overall pattern of safety and tolerability observed in the double-blind studies was as expected from the clinical experience with metformin and glyburide. No new or unexpected events or laboratory abnormalities were observed in this clinical program. Interim analyses of the long-term open-label extensions support the favorable safety profile observed in the short-term phase of the studies. In particular, the low dose fixed combination showed a favorable safety/tolerability profile when compared to the other regimens used in this program.

Detailed Description Text (68):

Double-blind, first line therapy demonstrated a statistically significant mean decrease in HemoglobinA.sub.1c (HbA.sub.1c) of 1.3% from placebo for both fixed combination treatment groups and a mean decrease from baseline of approximately 1.5%. While all active therapy treatment groups achieved acceptable glycemic control, greater mean decreases in HbA.sub.1c for both fixed combination treatment groups were achieved when compared to metformin therapy of glyburide therapy. Antihyperglycemic durability was observed with all active treatment groups (glyburide, metformin, metformin/glyburide 250/1.25 mg, metformin/glyburide 500/2.5 mg) as evidenced by the maintenance of the mean HbA.sub.1c levels from Week 20 (6.64%, 6.79%, 6.68%, 6.44%) to Week 32 (6.78%, 6.96%, 6.87%, 6.68%) of double-blind therapy below the therapeutic target of 7% (FIGS. 3 and 4).

Detailed Description Text (69):

Interim open-label first line therapy data demonstrate that for subjects directly enrolled, the mean HbA.sub.1c at baseline was 10.6%, and for the subset of subjects with available data, a mean decrease of 3.5% in HbA.sub.1c was achieved with a mean HbA.sub.1c of 7.1% through 26 weeks. Of the subjects directly enrolled into open-label therapy, 87% received the medium dose 500/2.5 mg fixed combination as initial therapy and at the time of the interim report, the mean dose of fixed combination therapy was metformin/glyburide 1569/7.85 mg. For subjects with available open-label data completing the double-blind treatment phase and continuing into the open-label treatment phase, the mean HbA.sub.1c at baseline was 8.32%. For all subjects reaching 13 weeks of therapy, a mean decrease of 1.76% in HbA.sub.1c was achieved with the mean HbA.sub.1c of 6.56%. Of the subjects completing the double-blind treatment phase and continuing into the open-label treatment phase, 78% received the low dose (250/1.25 mg) and 22% received the medium dose (500/2.5 mg) fixed combination as initial therapy. The mean dose of fixed combination therapy was metformin/glyburide 696/3.48 mg.

Detailed Description Text (70):

No clinically significant patterns of greater or reduced effect were apparent in any of the sub-populations (age, gender, race) with respect to response in HbA.sub.1c from baseline in either double-blind trial with fixed combination metformin/glyburide as first line therapy.

Detailed Description Text (71):

This clinical program also assessed fasting plasma glucose as a parameters of short term glycemic control. FPG results in double-blind studies were consistent with the HbA.sub.1c results. As first line therapy, statistically and clinically significant larger mean decreases in FPG for both fixed combination treatment groups compared to placebo and metformin were achieved (FIG. 6). An early response to fixed combination therapy was observed; differences among treatment groups were apparent by Week 2 of double-blind therapy as a time when subjects were still undergoing initial titration and were receiving only one-half potential maximum dosing. This early response at one-half maximum dosing in a monotherapy refractory patient population demonstrates the

benefit of combination therapy for the patient and using combination therapy earlier in the disease process.

Detailed Description Text (73):

As first line therapy, statistically significant larger mean decreases in absolute postprandial glucose (63-65 mg/dL) were observed for both fixed combination treatment groups than the placebo group. Larger mean decreases in absolute PPG were also achieved compared with glyburide (16-18 mg/dL) and metformin (18-20 mg/dL) monotherapy (FIGS. 8A and 8B). The 2-hour postprandial glucose excursion from a fasting baseline for both the low dose (22.5 mg/dL) and medium dose (23.9 mg/dL) fixed combination treatment groups was only 56%-59% of placebo (40.3 mg/dL), 59%-63% of glyburide (38.2 mg/dL) and 75%-81% of metformin (29.5 mg/dL). Evaluating the excursion rather than the absolute value demonstrates that glyburide is similar to placebo, metformin achieves better postprandial glucose lowering than glyburide and placebo, and that the low dose combination is the most powerful in lowering postprandial glucose excursion. As there is no published clinical data with combination therapy studied in a drug naive patient population, these results add new insight to understanding of the impact of treatment options at this stage of the disease. Indeed, the results could not have been predicted from the changes observed in the much studies second line therapy population.

Detailed Description Text (74):

Insulin levels were evaluated in the fasting and postprandial state in the first line therapy study (FIG. 7). There was a statistically significant increase in insulin response in the presence of a glucose load for both fixed combination treatment groups (24-28.8 .mu.iu/mL) compared to placebo. A larger increase in insulin response in the presence of a glucose load for the low dose fixed combination (14.6 .mu.iu/mL) treatment group was observed when compared to glyburide monotherapy and a larger increase in insulin response in the presence of a glucose load for both fixed combination (21-25.8 .mu.iu/mL) treatment groups was observed when compared to metformin monotherapy. When considering the mean doses of active therapy per treatment group, the insulin response cannot be explained by the sulfonylurea component alone with fixed combination therapy. This clinical data supports preclinical work with isolated pancreatic islet cells where it has been suggested that metformin prevents the hyperglycemic desensitization of the islet cells. The combination of the physiologic and appropriate increased insulin response with a corresponding larger decrease in glucose excursion suggests that the combination is improving the efficiency of the pancreas in responding to a glucose load, preserving beta cell function and improving insulin sensitivity.

Detailed Description Text (75):

The essential goal in the management of patients with type 2 diabetes, in addition to aggressively treating elevated blood pressure and lipid levels, is achieving as near normal glycemic levels as possible or achieving glycemic therapeutic targets. There was a greater response to fixed combination therapy with respect to greater frequencies of subjects achieving therapeutic targets and greater decreases in absolute HbA.sub.1c. As first line therapy, a higher frequency of subjects on fixed combination therapy (66%-71%) achieved a glycemic target of an HbA.sub.1c <7% compared with 60% of sulfonylurea monotherapy, 50% of metformin monotherapy and 20% of placebo following 20 weeks of double-blind therapy. Approximately 28% of subjects in each fixed combination group had decreases in HbA.sub.1c from baseline greater than 2.0%, compared with 16%-17% of each monotherapy group and 3% of placebo. Of note, is that these targets were not achieved with simply higher total doses of medication, but with lower doses of the complementary components. Mean final doses achieved in each first line therapy treatment arm were approximately glyburide 5.3 mg, metformin 1307 mg, low dose fixed combination 557/2.78 mg and medium dose fixed combination 818/4.1 mg. For the change in HbA.sub.1c by number of tablets, the pattern observed with fixed combination therapy is not unexpected from a pathophysiologic viewpoint. It indicates that there is a clear response to target at all dose levels and that the need for higher doses correlates with a higher baseline HbA.sub.1c. A similar pattern can be detected for glyburide up to a total dose 7.5 mg; no clear pattern was observed with metformin therapy.

Detailed Description Text (76):

The data presented supports low dose fixed combination metformin/glyburide as the first line agent most likely to bring a patient to therapeutic target, no matter how high their baseline HbA.sub.1c. For both fixed combination therapies, the mean decrease from baseline HbA.sub.1c is larger for subjects with higher baseline levels. This phenomenon was not observed with glyburide, metformin or placebo and is not expected to be seen with other monotherapies. This demonstrates the contribution of components necessary for achieving therapeutic glycemic targets when baseline HbA.sub.1c level is greater

than 9%. Monotherapy was shown to have a plateauing of glycemic response for baseline HbA.sub.1c levels <9% while fixed combination therapy had additional incremental decreases in HbA.sub.1c for baseline HbA.sub.1c levels <9%.

Detailed Description Text (78):

Weight gain is typically observed with all antihyperglycemic agents other than metformin monotherapy. With improved glycemic control, a weight gain is actually expected as calories are conserved rather than lost due to poor metabolic control. In this clinical program, as glycemic control improved, minimal early weight gain of approximately 1-2 kg was observed with fixed combination therapy; this was comparable to the 2 kg weight gain observed with first line glyburide monotherapy. In double-blind therapy, after the initial minimal gain, weight remained stable and did not continue to increase with time.

Detailed Description Text (79):

Overall there were no clinically or statistically significant differences between any of the treatment groups with respect to changes in the plasma lipid profile. As the most severe patients were excluded from the placebo controlled trial, smaller changes in response to therapy might be undetectable. The first line therapy patient population had inadequate glycemic control but diet and exercise has already succeeded in bringing the mean HbA.sub.1c to 8.2%. In subjects treated with fixed combination therapy, there was no adverse effect on the plasma lipid profile (total cholesterol, LDL, HDL, and triglycerides) or significant differences compared with placebo or either glyburide and metformin monotherapy.

Detailed Description Text (81):

Low dose fixed combination metformin/glyburide therapy is safe and effective in achieving and maintaining glycemic control in patients with type 2 diabetes who have inadequate glycemic control with diet and exercise. The use of combination therapy earlier in the diabetes disease progression appears to be a clinically sound alternative to the classic treatment paradigms of allowing failure of step wise therapy before instituting a more aggressive, but clinically sound, treatment strategy. Though not evaluated in this short-term study, the strategy to achieve as near normal glycemic targets as possible is likely to have an impact in slowing the progression of the diabetes disease process and delay the onset of long-term diabetes complications. Given a refractory monotherapy patient population the fixed combination of metformin and glyburide was associated with a clinically significant improvement in glycemic control without evidence of detrimental metabolic effects or safety concerns. There was no clinically significant hypoglycemia, no negative impact in plasma lipids and a limited early weight gain followed by stable weight with time. The synergism of the metformin and sulfonylurea combination is an established one; a fixed combination of metformin and glyburide is effective in improving glycemic control and is a rationale choice in the antihyperglycemic armamentarium. It is assumed that a fixed combination simplifies dosing, is more convenient and therefore may lead to better compliance with therapy.

Detailed Description Text (84):

The safety and efficacy data presented from this clinical program assessing fixed combination metformin/glyburide as first line therapy in patients with type 2 diabetes confirm the following: The percentages of subjects who discontinue from therapy because of hyperglycemia were lower for fixed combination metformin/glyburide compared with metformin, glyburide, and placebo. Hypoglycemia and symptoms of hypoglycemia, as first line therapy (FIG. 9), occurred less often with metformin/glyburide 250/1.25 mg compared to metformin/glyburide 500/2.5 mg and glyburide. As first line therapy, the incidence of gastrointestinal adverse events associated with fixed combination was lowest for metformin/glyburide 250/1.25 mg compared with metformin/glyburide 500/2.5 mg and metformin (FIG. 10). No new or unexpected adverse events or laboratory abnormalities occurred in subjects who received long-term open-label fixed combination metformin/glyburide. Significantly better efficacy of fixed combination metformin/glyburide at any dose strength as evidenced by greater reductions of all glycemic parameters (HbA.sub.1c, postprandial glucose, fasting glucose and fructosamine) compared to placebo, glyburide and metformin therapy. A synergistic effect of the low dose combination in targeting multiple metabolic defects to improve beta cell function and insulin sensitivity, as evidenced by postprandial plasma glucose and insulin excursions, to achieve improved metabolic function and glycemic control. A higher frequency of patients on fixed combination metformin/glyburide therapy achieved a glycemic therapeutic target of an HbA.sub.1c.ltoreq.7%. Efficient glycemic lowering to therapeutic targets for any baseline HbA.sub.1c compared with placebo, glyburide and metformin therapy. As initial therapy, glyburide and metformin were shown to have a plateauing of glycemic response for baseline HbA.sub.1c levels >9% while fixed

combination metformin/glyburide therapy had additional incremental decreases in HbA.sub.1c for baseline HbA.sub.1c levels >9%. Limited early weight gain paralleling improved glycemic control, comparable to glyburide monotherapy; however, weight remained stable with time. No adverse effect of the fixed combination therapies on the lipid profile (total cholesterol, LDL, HDL, and triglycerides) or significant differences from placebo or either glyburide and metformin monotherapy. The favorable efficacy and tolerability of fixed combination metformin/glyburide 250/1.25 mg supports its use as the initial starting dose in first line therapy.

Detailed Description Text (85):

The above results clearly show that treating diabetes with the low dose metformin/glyburide formulation of the invention (250 mg/1.25 mg) is at least equivalent in efficacy to the higher dosage form (500 mg/2.5 mg), while resulting in reduced side effects.

Detailed Description Paragraph Table (1):

Composition of Metformin Hydrochloride-Glyburide Tablets 250 mg/1.25 mg and 500 mg/2.5 mg  
 Example 1 Example 2  
 QUANTITY PER TABLET (mg) INGREDIENT 250 mg/1.25 mg 500 mg/2.5 mg  
 Metformin Hydrochloride 250.0 500.0 Glyburide 1.25 2.5 Croscarmellose Sodium 7.00 14.0  
 Povidone 10.00 20.0 Microcrystalline Cellulose 28.25 56.5 Magnesium Stearate 2.25 4.5  
 Film Coat\* 6 12 \*HPMC based film coat used.

Other Reference Publication (4):

Hermann et al, Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care, 17:1100-1109 (1994).

Other Reference Publication (17):

Vigneri et al, "Treatment of NIDDM Patients with Secondary Failure to Glyburide: Comparison of the Addition of Either Metformin or Bed-Time NPH Insulin to Glyburide", Diabete & Metabolisme, 1991, 17, 232-234.

Other Reference Publication (18):

Higginbotham et al, "Double-Blind Trial of Metformin in the Therapy of Non-Ketotic Diabetes", The Med. Journal of Australia, Aug. 11, 1979, 154-156.

Other Reference Publication (19):

Edwards et al, Combination Glipizide/Metformin Treatment Reduces Low Density Lipoprotein Binding to Arterial Proteoglycane in NIDDM, Diabetes, (46, Suppl. 1, 45A, 1997).

Other Reference Publication (20):

Cefalu et al, "Combination of glipizide/Metformin Normalizes Glucose and Improves Insulin Sensitivity in Hyperinsulinemia Moderately Well Controlled", Diabetes (45, Suppl. 2, 201A, 1996).

Other Reference Publication (21):

Crouse et al, "Effects of Combination of Glipizide/Metformin Treatment on Oxidizability of LDL in NIDDM", Circulation (94, No. 8, Suppl., 1508, 1996).

Other Reference Publication (22):

Cefalu et al, "Insulin Sensitivity is Improved After Glipizide Monotherapy and Combination with Metformin", Diabetologia (39, Suppl. 1, A231, 1996).

Other Reference Publication (23):

Reaven et al, "Combined Metformin-Sulfonylurea Treatment of Patients with Noninsulin-Dependent Diabetes in Fair to Poor Glycemic Control", J. Clin. Endocrinol. Metab. (74, No. 5, 1020-26, 1992).

Other Reference Publication (24):

Hollenbeck et al, "Combination Glipizide/Metformin Treatment in Non-Insulin Dependent Diabetes (NIDDM)", Diabetes (39, Suppl. 1, 108A, 1990).

Other Reference Publication (31):

Haupt et al, "Oral Antidiabetic Combination Therapy with Sulfonyl Ureas and Metformin", Med. Welt. (40, No. 5, 118-23, 1989).

CLAIMS:

1. A method for first line treatment of type 2 diabetes in a drug naive human patient, which comprises administering a drug to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a pharmaceutical formulation comprising a low dose combination of metformin and at least one or more other antidiabetic agent, which is one or more of a glucosidase inhibitor, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR .alpha./.gamma. dual agonist other than a thiazolidinedione, a meglitimide and an aP2 inhibitor, which provides at least substantially equivalent efficacy in treating diabetes in drug naive patients, but with substantially reduced side effects, as compared to metformin and said other antidiabetic agent employed in substantially higher daily dosages, wherein the dose of metformin is in an amount to provide a daily dosage within the range from about 160 mg to about 750 mg.

4. A method for lowering blood glucose in a hyperglycemic human patient, which comprises administering to a human patient in need of treatment a therapeutically effective amount of a low dose pharmaceutical formulation comprising a low dose combination of metformin and at least one or more other antidiabetic agent, which is one or more of a glucosidase inhibitor, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR .alpha./.gamma. dual agonist other than a thiazolidinedione, a meglitimide and an aP2 inhibitor, which provides at least substantially equivalent efficacy in treating diabetes in drug naive patients, but with substantially reduced side effects, as compared to combinations of metformin and the other antidiabetic agent, employed in substantially higher daily dosages, wherein the dose of metformin is in an amount to provide a daily dosage within the range from about 160 mg to about 750 mg.

5. A method for decreasing insulin resistance, decreasing hemoglobinA.sub.1c, increasing post-prandial insulin levels or decreasing post-prandial glucose excursion, in a diabetic human patient, which comprises administering to a human patient in need of treatment a low dose pharmaceutical formulation comprising a low dose combination of metformin and at least one or more other antidiabetic agent, which is one or more of a glucosidase inhibitor, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR .alpha./.gamma. dual agonist other than a thiazolidinedione, a meglitimide and an aP2 inhibitor, which provides at least substantially equivalent efficacy in treating diabetes in drug naive patients, but with substantially reduced side effects, as compared to combinations of metformin and the other antidiabetic agent, employed in substantially higher daily dosages, wherein the dose of metformin is in an amount to provide a daily dosage within the range from about 160 mg to about 750 mg.

7. The method as defined in claim 4 wherein the metformin is said low dose formulation is administered in an amount within the range from about 160 to about 400 mg 1 to 4 times daily, with a maximum daily dosage of metformin of about 750 mg and a minimum daily dosage of metformin of about 225 mg.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw	Desc	Image							

RWD

☐ 13. Document ID: US 6559188 B1

L2: Entry 13 of 14

File: USPT

May 6, 2003

DOCUMENT-IDENTIFIER: US 6559188 B1

TITLE: Method of treating metabolic disorders especially diabetes, or a disease or condition associated with diabetes

Abstract Text (2):

or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition; the use of such combination or composition for

the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; the use of such combination or composition for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; and to a method of improving the bodily appearance of a warm-blooded animal.

Brief Summary Text (1):

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; the use of such combination for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; a method of improving the bodily appearance of a warm-blooded animal; to a pharmaceutical composition which comprises nateglinide as the sole active agent in the composition and a pharmaceutically acceptable carrier and to a process of making such pharmaceutical composition.

Brief Summary Text (4):

or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use, particularly in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes mellitus and diseases and conditions associated with diabetes mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition.

Brief Summary Text (5):

By the term "a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use", there is meant especially a "kit of parts" in the sense that the components nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the components. Preferably, there is at least one beneficial effect, e.g. a mutual enhancing of the effect of nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl ureas and metformin, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or each of the components nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin, and especially a strong synergism between nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin.

Brief Summary Text (7):

By the term "a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide and an antidiabetic thiazolidinedione derivative, wherein each of the active ingredients are present in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, as a combined preparation for simultaneous, separate or sequential use", there is meant

especially a "kit of parts" in the sense that the components nateglinide and the antidiabetic thiazolidinedione derivative can be dosed independently or by use of different fixed combinations with distinguished amounts of the components at different time points. Preferably, there is at least one beneficial effect, e.g. a mutual enhancing of the effect of nateglinide and the antidiabetic thiazolidinedione derivative, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or each of the components nateglinide and the antidiabetic thiazolidinedione derivative, especially a strong synergism between nateglinide and the anti-diabetic thiazolidinedione derivative.

#### Brief Summary Text (13):

A sulphonyl urea derivative is, for example, glisoxepid, glyburide, acetoexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably glimepiride or gliclazide.

#### Brief Summary Text (19):

Nateglinide (EP 196222, EP 526171, U.S. Pat. Nos. 5,463,116 and 5,488,150), 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]benzoic acid (repaglinide, U.S. Pat. No. 5,216,167--also known as (S)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]-amino]-2-oxoethyl}benzoic acid); 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}-thiazolidine-2,4-dione (pioglitazone, EP 0 193 256 A1), 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone, EP 0 306 228 A1), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone, EP 0 139 421), (S)-((3,4-dihydro-2-(phenyl-methyl)-2H-1-benzopyran-6-yl)methyl)-thiazolidine-2,4-dione (englitazone, EP 0 207 605 B1), 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethylbenzyl)benzamide (KRP297, JP 10087641-A), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]thiazolidine-2,4-dione (MCC555, EP 0 604 983 B1), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone, EP 0 332 332), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637, U.S. Pat. No. 4,997,948) and 5-{[4-(1-methyl-cyclohexyl)methoxy]-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone, U.S. Pat. No. 4,287,200) are generically and specifically disclosed in the documents cited in brackets beyond each substance, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims is hereby incorporated into the present application by reference to this publications. Comprised are likewise the corresponding stereoisomers as well as the corresponding crystal modifications, e.g. solvates and polymorphs, which are disclosed therein. The term nateglinide as used herein comprises crystal modifications (polymorphs) such as those disclosed in EP 0526171 B1 or U.S. Pat. No. 5,488,510, respectively, the subject matter of which is incorporated by reference to this application, especially the subject matter of claims 8 to 10 as well as the corresponding references to the B-type crystal modification. Preferably, in the present invention the B- or H-type, more preferably the H-type, is used.

#### Brief Summary Text (21):

Furthermore, MCC555 can be formulated as disclosed on page 49, lines 30 to 45, of EP 0 604 983 B1; englitazone as disclosed from page 6, line 52, to page 7, line 6, or analogous to Examples 27 or 28 on page 24 of EP 0 207 605 B1; and darglitazone and 5-{[4-(2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246) can be formulated as disclosed on page 8, line 42 to line 54 of EP 0 332 332 B1. AY-31637 can be administered as disclosed in column 4, lines 32 to 51 of U.S. Pat. No. 4,997,948 and rosiglitazone as disclosed on page 9, lines 32 to 40 of EP 0 306 228 A1, the latter preferably as its maleate salt.

#### Brief Summary Text (22):

Corresponding to the needs of the single patient and under the proviso that it is intended by a physician to administer the combinations, e.g. the pharmaceutical compositions, in separate tablets, it is possible to administer the antidiabetics as launched, e.g. rosiglitazone in the form as it is launched under the trademark AVANDIA.TM.. Troglitazone can be administered in the form as it is launched under the trademarks ReZulin.TM., PRELAY.TM., ROMOZIN.TM. (in the United Kingdom) or NOSCAL.TM.

(in Japan). Pioglitazone can be administered as disclosed in Example 2 of EP 0 193 256 A1, preferably in the form of the monohydrochloride salt or in the form as launched under the trademark ACTOS.TM.. Ciglitazone can, for example, be formulated as disclosed in Example 13 of U.S. Pat. No. 4,287,200. If the drug metformin shall be administered in a separate pharmaceutical composition, it can be administered in the form as it is launched e.g. under the trademark DIABETOSAN.TM.. If the drug metformin shall be administered in a separate pharmaceutical composition in the form of its hydrochloride salt, the metformin hydrochloride salt can be administered in the form as it is launched e.g. under the trademarks DIABETASE 500.TM., DIABETASE 850.TM. or GLUCOPHAGE S.TM.. Glyburide can be taken in the form as it is launched under the trademark AZUGLUCON.TM. or EUGLUCON.TM.. Tolbutamide can be administered in the form as it is launched under the trademark ORABET, glimepiride as launched under the trademark AMARYL.TM., gliclazide as launched under the trademark DIAMICRON.TM., glibornuride as launched under the trademark GLUBORID.TM. and gliquidone as it is launched under the trademark GLURENORM.TM..

Brief Summary Text (24):

The recommended dose for rosiglitazone taken as a single drug is 4 mg or 8 mg administered either as a single dose or in divided doses twice daily. The best responses with rosiglitazone in the treatment of diabetes are observed with 4 mg twice daily. The recommended dose for pioglitazone taken as a single drug is 15 mg, 30 mg or 45 mg taken once daily.

Brief Summary Text (26):

All the more surprising is the experimental finding that the combined administration of nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, in particular rosiglitazone, troglitazone and pioglitazone, sulfonyl urea derivatives and metformin results not only in a beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the combined treatment and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

Brief Summary Text (28):

It can be shown by established test models and especially those test models described herein that the combination of nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, in particular rosiglitazone, rosiglitazone and pioglitazone, sulfonyl urea derivatives and the biguanide metformin, or in each case a pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of diseases, especially metabolic disorders, and in particular type 2 diabetes mellitus and diseases and conditions associated with diabetes mellitus. In particular, it can be shown by established test models and especially those test models described herein that the combination of nateglinide and an antidiabetic thiazolidinedione derivative, or in each case a pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of diseases, especially metabolic disorders, more especially diabetes and in particular type 2 diabetes mellitus, and diseases and conditions associated with diabetes.

Brief Summary Text (34):

These studies prove in particular the synergism of the claimed combinations, such as the combined preparations or pharmaceutical compositions, respectively. The beneficial effects on diseases and conditions associated with diabetes mellitus as defined in this application can be determined directly through the results of these studies or by changes in the study design which are known as such to a person skilled in the art.

Brief Summary Text (35):

The studies are, in particular, suitable to assess the effects of monotherapy with nateglinide, repaglinide, a glitazone, a sulfonyl urea derivative or metformin and a combination of nateglinide or repaglinide with one or more compounds selected from the group consisting of a glitazone, a sulfonyl urea derivatives or metformin on glycemic control. The studies are especially suitable to assess the effects of monotherapy with metformin or the corresponding hydrochloride salt or a combination of nateglinide and metformin or the corresponding hydrochloride salt on glycemic control. Subjects with a diagnosis of type 2 diabetes who have not achieved near normoglycemia (HbA.sub.1c <6.8%) on diet only are chosen for this trial. The effects on glycemic control achieved with nateglinide monotherapy, monotherapy with a glitazone, monotherapy with metformin and the combination therapies as given below are determined in these studies after 16 or 24 weeks with the control achieved on placebo, all subjects continuing with the same

diet as in the period before treatment. Measures of glycemic control are validated surrogate endpoints for the treatment of diabetes. HbA.sub.1c is the single most reliable measurement for assessing glycemic control (D. Goldstein et al, Tests of Glycemia in Diabetes; Diabetes Care 1995, 18(6), 896-909) and is the primary response variable in these studies. Since glycosylation of hemoglobin is determined by the glucose concentration at the time each red blood cell is made, HbA.sub.1c provides an estimate of mean blood glucose for the previous three months.

Brief Summary Text (43):

Study 3: Combination of 60 mg Nateglinide and 250 mg of Metformin Administered as a Single Pharmaceutical Composition

Brief Summary Text (45):

Study 4: Combination of 60 or 120 mg Nateglinide Before Meals and 1000 mg of Metformin as a Daily Dosis

Brief Summary Text (46):

Subjects with HbA.sub.1c values of 6.8-11% receive metformin for at least 3 months und at least 1500 mg/day during the last 4 weeks before starting period 0. After period 0 extending over 4 weeks in which period 1000 mg/day metformin plus nateglinide placebo are given to the subjects, the subjects are randomised to nateglinide placebo, 60 mg nateglinide or 120 mg nateglinide before main meals for 24 weeks while continuing to receive 1000 mg metformin daily.

Brief Summary Text (50):

The combined administration of nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin results in a beneficial, especially a synergistic, therapeutic effect, especially on type 2 diabetes, and also in additional benefits such as a decrease of diabetes-related mortality, a surprising prolongation of efficacy of the drug (such delaying the eventual need for insulin), a broader variety of therapeutic treatment, maintaining the target blood glucose level in type 2 diabetes patients, providing a good initial blood glucose control in type 2 diabetes patients, only modest changes in fasting plasma glucose level, and further surprising beneficial effects, comprising e.g. less or no gain of body weight, a decrease of gastrointestinal side effects or an improved safety profile, compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein. In particular, the further surprising beneficial effects can also be observed during the treatment of metabolic disorders other than type 2 diabetes and during the treatment of diseases and conditions associated with type 2 diabetes. Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects (e.g. anaemia, oedema, headache).

Brief Summary Text (52):

The beneficial therapeutic effect, additional benefits and especially the surprising beneficial effects are observed in particular with nateglinide. Very good results have been obtained with the combination of nateglinide and metformin or metformin hydrochloride.

Brief Summary Text (54):

In one preferred embodiment of the invention, a dose of between 45 and 85 mg, more preferably 60 mg, of nateglinide per meal is administered as part of the combination to human subjects having a HbA.sub.1c value at baseline between 6.8% and 8%, in particular between 6.8% and 7%. This provides the option to increase the amount of nateglinide later on, which option is advantageous especially in a situation when the HbA.sub.1c value at baseline exceeds values of 7% after starting the treatment of the human subject for a period of time or constantly or if the responsible physician determines that the treatment schedule has to be changed to higher amounts of nateglinide for other reasons. One preferred combination partner in this embodiment is metformin.

Brief Summary Text (60):

In one preferred embodiment of the invention the combination comprising nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and comprises further insulin or that the combination comprises at least two antidiabetic compounds selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin, or a pharmaceutically acceptable salt thereof.

Brief Summary Text (61):

Also preferred is a combination in which said other antidiabetic compound is metformin or metformin hydrochloride or is selected from the group of glitazones, especially rosiglitazone or troglitazone, or in particular, pioglitazone.

Brief Summary Text (80):

A very preferred glitazone according to all aspects of the present invention is selected from the group consisting of rosiglitazone, MCC555, troglitazone and especially pioglitazone, and their pharmaceutically acceptable salts. In the case of pioglitazone the invention relates in particular to the monohydrochloride salt.

Brief Summary Text (83):

In a very preferred embodiment of the invention nateglinide is administered in combination with metformin, metformin hydrochloride or a mixture thereof. Nateglinide and metformin, metformin hydrochloride or a mixture thereof can be administered at different points in time, e.g. nateglinide before breakfast, lunch and dinner and metformin, metformin hydrochloride or a mixture thereof after breakfast, lunch and dinner, or simultaneously. Preferably, nateglinide and metformin, metformin hydrochloride or a mixture thereof are administered simultaneously. Very preferably, nateglinide and metformin, metformin hydrochloride or a mixture thereof are administered thrice daily before breakfast, lunch and dinner. It is also very preferred to administer nateglinide and metformin, metformin hydrochloride or a mixture thereof together in fixed combination.

Brief Summary Text (84):

It is one objective of this invention to provide a pharmaceutical composition comprising an amount, which is jointly therapeutically effective against metabolic disorders, in particular type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus, of (i) nateglinide or repaglinide or in each case a pharmaceutically acceptable salt thereof and (ii) and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. In this composition, components (i) and (ii) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. Preferably, the unit dosage form is a fixed combination. Preferably, a pharmaceutical composition of the present invention comprising nateglinide comprises the B- or H-type crystal modification of nateglinide, more preferably the H-type.

Brief Summary Text (86):

Furthermore, the invention relates to a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide and a glitazone, wherein the combined preparation or pharmaceutical composition, respectively, comprises at least one further pharmaceutically active compound e.g. selected from the group consisting of a sulphonyl urea derivative, a pharmaceutically acceptable salt thereof, metformin and insulin; or wherein the combined preparation or pharmaceutical composition, respectively, comprises at least one further glitazone or a pharmaceutically acceptable salt thereof.

Brief Summary Text (87):

A further aspect of the present invention is the use of a pharmaceutical composition comprising nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin in each case in free form or in form of a pharmaceutically acceptable salt thereof for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus. In particular, this further aspect of the present invention relates to the use of a pharmaceutical composition comprising nateglinide and a glitazone in each case in free form or in form of a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical preparation for the prevention or treatment of diseases, especially metabolic disorders, more especially diabetes and in particular type 2 diabetes mellitus, and diseases and conditions associated with diabetes.

Brief Summary Text (88):

Furthermore, the invention relates to a pharmaceutical composition comprising nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin in each

case in free form or in form of a pharmaceutically acceptable salt thereof for the prevention, delay of progression or treatment of hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and in particular conditions of impaired glucose tolerance and especially type 2 diabetes.

Brief Summary Text (91):

The term "combination therapy" as used herein means that a combination which comprises nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin, is used for the treatment, delay of progression or prevention of one of the diseases, especially metabolic disorders, mentioned herein.

Brief Summary Text (109):

In accordance with the methods of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. For example, in a two-component combination of, e.g., nateglinide or repaglinide and/or a glitazone as herein defined or metformin, treatment with nateglinide or repaglinide can commence prior to, subsequent to or concurrent with commencement of treatment with the glitazone and/or the metformin. Furthermore, the term administering also encompasses the use of prodrugs of any of the anti-diabetic drugs that convert in vivo to the selective anti-diabetic drug. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

Brief Summary Text (117):

Nateglinide or repaglinide will suitably be present in the compositions of the invention in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising an additional component metformin, this will generally be present in an amount of from about 1 to about 90% by weight, more commonly from about 5 or 10 to about 70% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising an additional component thiazolidinone derivative, this will generally be present in an amount of from about 2 to about 50% by weight based on the total weight of the composition.

Brief Summary Text (121):

Especially, the present invention relates to a pharmaceutical composition for combination therapy comprising nateglinide and metformin in a pharmaceutical carrier, which is preferably in the form of a tablet, a capsule, a suspension or a liquid. Such pharmaceutical composition contains most preferably from about 100 mg to about 130 mg of nateglinide and from about 320 mg to about 1500 mg, more preferably 330 mg to 350 mg, metformin per dose unit.

Brief Summary Text (125):

A further aspect of the present invention is a method of treating a warm-blooded animal, especially a human, having metabolic disorders, in particular type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus, comprising administering to the animal a combination of nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin in an amount which is jointly therapeutically effective against metabolic disorders in which both compounds can also be present in the form of their pharmaceutically acceptable salts. Preferably, such a method of treating is carried out with nateglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin contained in the same dosage unit form. The combination is preferably administered simultaneously.

Brief Summary Text (126):

In particular, the present invention relates to a method of treating diabetes or a disease or condition associated with diabetes comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of nateglinide in free or pharmaceutically acceptable salt form, and a glitazone, in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order,

separately or in a fixed combination. Preferably, in this method nateglinide and the glitazone are provided as a combined preparation. In one preferred embodiment, this method further comprises administration of a therapeutically effective amount of at least one further pharmaceutically active compound selected from the group consisting of sulphonyl urea derivatives, a pharmaceutically acceptable salt thereof, metformin and insulin; or at least one further glitazone, or a pharmaceutically acceptable salt thereof. Preferably, in this method the glitazone is a compound of formula (II), wherein A represents naphthyl, benzoxazolyl, dihydrobenzopyranyl, indole, phenyl (optionally substituted by halogen) or phenylethynyl (optionally substituted by halogen); R.sub.1 represents halogen or a radical --XR.sub.4, in which X can be oxygen, lower alkyl, carbonyl or --NH--, R.sub.4 is naphthyl; phenyl, unsubstituted or substituted by 2,4-dioxo-5-thiazolidinyl; or lower alkyl or hydroxy lower alkyl, unsubstituted or substituted by a) indole or 2,3-dihydroindole, b) pyridyl, lower alkyl-pyridyl, N-lower alkyl-N-pyridylamino or halogenphenyl, c) dihydrobenzopyranyl, which is unsubstituted or substituted by hydroxy and lower alkyl, d) oxazolyl, which is substituted by lower alkyl and phenyl, e) cycloalkyl, which is unsubstituted or substituted by lower alkyl, or f) arylcycloalkylcarbonyl; R.sub.2 represents hydrogen or trifluoromethylphenyl-lower alkyl carbamoyl; and R.sub.3 represents hydrogen or arylsulfonyl. In a first more preferred embodiment of this method, the glitazone is selected from the group consisting of englitazone, darglitazone, ciglitazone, DRF2189, BM-13.1246, AY-31637, YM268, AD-5075, DN-108, 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-{[3-(4-chlorophenyl)]-2-propynyl]-5-phenylsulfonyl}thiazolidine-2,4-dione, and 5-{[3-(4-chlorophenyl)]-2-propynyl]-5-(4-fluorophenylsulfonyl}thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof. In a second more preferred embodiment of this method, the glitazone is selected from the group consisting of rosiglitazone, pioglitazone, troglitazone, and MCC555 or a pharmaceutically acceptable salt thereof. In a second more preferred embodiment of this method, the glitazone is selected from the group consisting of T-174 and KRP297 or a pharmaceutically acceptable salt thereof.

#### Brief Summary Text (127):

Especially, the present invention relates to a method of treating diabetes or a disease or condition associated with diabetes comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of nateglinide in free or pharmaceutically acceptable salt form, and a glitazone, in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, separately or in a fixed combination, which method further comprises administration of a therapeutically effective amount of at least one further pharmaceutically active compound selected from the group consisting of sulphonyl urea derivatives, a pharmaceutically acceptable salt thereof, metformin and insulin; or at least one further glitazone or a pharmaceutically acceptable salt thereof. This particular embodiment of the invention relates especially to a method of treating type 2 diabetes patients by using an effective amount of a combination of at least one short-acting hypoglycemic agent with at least one other longer-acting hypoglycemic agent, in an amount sufficient to treat post-prandial hyperglycemia. Preferably, the short acting hypoglycemic agent is nateglinide. Also preferably, the long acting hypoglycemic agent is metformin. In an alternate preferred embodiment, the long acting hypoglycemic agent is a glitazone, most preferably 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione; rosiglitazone, pioglitazone, troglitazone, MCC555; T-174; KRP297; englitazone, darglitazone, ciglitazone, AY-31637, 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, BM-13.1246, bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-{[3-(4-chlorophenyl)]-2-propynyl]-5-phenylsulfonyl}thiazolidine-2,4-dione, 5-{[3-(4-chlorophenyl)]-2-propynyl]-5-(4-fluorophenylsulfonyl}thiazolidine-2,4-dione; or 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108); or a pharmaceutically acceptable salt thereof. In the present embodiment, the short acting hypoglycemic and the long acting hypoglycemic agent are contained in the same dosage unit.

#### Brief Summary Text (129):

The ratio of the daily doses of nateglinide or repaglinide or a pharmaceutically acceptable salt thereof to the glitazone, sulfonyl urea derivative or metformin or in each case a pharmaceutically acceptable salt thereof may vary within wide limits especially depending of the nature of the compounds selected. In order to obtain a synergistic effect of the components, preferably the ratio of nateglinide or a pharmaceutically acceptable salt thereof to the glitazone is between 12000:1 and 1:2800, more preferably between 500:1 and 1:100, for example between 1.5:1, and between 400:1 and 2:1 in case of rosiglitazone; and between 50:1 and 1:3 in case of

pioglitazone. The ratio of nateglinde to rosiglitazone is preferably between 50:1 and 20:1, e.g. 22.5:1 or 45:1. The ratio of nateglinde to pioglitazone is preferably between 30:1 and 3:1, e.g. 24:1, 12:1 or 8:1.

Brief Summary Text (130):

In one preferred embodiment of the invention the ratio of the daily doses of nateglinde to metformin is between 1:3.5 and 1:40, preferably 1:4 and 1:7.1, and very preferably between 1:4.1 and 1:4.5, for example 1:4.2. In a further preferred embodiment of the invention the ratio of the daily doses of nateglinde to metformin is between 1:2 and 1:3.

Brief Summary Text (131):

In one preferred embodiment of the invention the ratio of the daily doses of nateglinde to metformin hydrochloride is between 1:1.25 and 1:9, more preferably between 1:2.5 and 1:5, e.g. 1:4.2. In a further preferred embodiment of the invention the ratio of the daily doses of nateglinde to metformin hydrochloride is between 4:1 and 1:1, more preferably between 2.5:1 and 1.5:1, e.g. 2:1. In another preferred embodiment of the invention the ratio of the daily doses of nateglinde to metformin hydrochloride is between 25:1 and 4.5:1, more preferably between 20:1 and 8:1, in particular 18:1, 16:1, 14:1, 10:1 and especially 12:1.

Brief Summary Text (139):

If the warm-blooded animal is a human the dosage of MCC555 is preferably in the range of about 0.1 to 2000, more preferably about 0.25 to 500, and most preferably 0.5 to 100, mg/day, per adult patient. The dosage of englitazone or darglitazone is preferably in the range of about 0.05 to 50, more preferably about 0.05 to 5, mg/kg body weight of the patient per day, if the warm-blooded animal is a human. The dosage of AY-31637 is in the range of about 0.5 to 200, more preferably about 2.5 to 100, mg/kg body weight of the patient per day, if the warm-blooded animal is a human. The dosage of ciglitazone is in the range of about 0.25 to 200, more preferably about 0.5 to 50, mg/kg body weight of the patient per day, if the warm-blooded animal is a human. The dosage of DN-108 is in the range of about 0.25 to 200, more preferably about 5 to 100, mg/kg body weight of the warm-blooded animal. If the antidiabetic thiazolidinedione is T-174, KRP297, AD-5075, 5-[3-(4-chlorophenyl)-2-propynyl]-5-phenylsulfonyl-thiazolidine-2,4-dione or 5-[3-(4-chlorophenyl)-2-propynyl]-5-(4-fluoro-phenylsulfonyl)thiazolidine-2,4-dione, the dosage of said compound is preferably in the range of about 0.1 to 2500, more preferably about 0.5 to 2000, and most preferably 1 to 1000, mg/day. If the antidiabetic thiazolidinedione is rosiglitazone, the dosage of said compound is in case of the warm-blooded animal being a human of about 70 kg body weight preferably in the range of about 0.1 to 500, more usually about 0.5 to 100, and most preferably 1 to 20, for example 1, 2, 4 or 8, mg/day, per adult patient. If the warm-blooded animal being is a human of about 70 kg body weight, the dosage of pioglitazone is preferably in the range of about 0.1 to 1000, more usually about 1 to 500, and most preferably 10 to 150, for example 15, 30, 45 or 90, mg/day, per adult patient.

Brief Summary Text (140):

In one preferred embodiment, the active ingredient is metformin, the warm-blooded animal being is a human of about 70 kg body weight and the dosage of said compound is preferably in the range of about 750 to 2000, and most preferably 1000 to 1500, mg/day, per adult patient. In one preferred embodiment of the invention, 180 mg of nateglinde and 750 mg of metformin are given as a daily dose to a human patient of about 70 kg body weight. In a further preferred embodiment of the invention, the active ingredient metformin shall be applied in the form of metformin hydrochloride in a dosage between 1500 and 3000, especially 1500, 1700 or 2550 mg/day to a warm-blooded animal of about 70 kg body weight. In another preferred embodiment, the active ingredient metformin shall be applied in the form of metformin hydrochloride in a dosage between 700 and 1250, especially between 750 and 1100, e.g. 1000, mg/day to a warm-blooded animal of about 70 kg body weight.

Brief Summary Text (141):

If the sulfonyl urea derivative glyburide is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 0.5 to 20, more preferably 1.75 to 15, for example 3.5, 7.0 or 10.5, mg/day. If the sulfonyl urea derivative tolbutamide is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 100 to 3500, more preferably 250 to 3000, for example 500, 1000, 1500, 2000, 2500, mg/day. If the sulfonyl urea derivative glimepiride is chosen as active ingredient and the

warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 0.25 to 12, more preferably 0.5 to 10 and most preferably between 1 and 3, mg/day. If the sulfonyl urea derivative gliclazide is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 5 to 500, more preferably 15 to 300 and most preferably between 40 and 120, mg/day. If the sulfonyl urea derivative glubomuride is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 5 to 250, more preferably 12.5 to 75 and most preferably between 12.5 and 50, mg/day. If the sulfonyl urea derivative gliquidone is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the dosage of said compound is preferably in the range of about 5 to 500, more preferably 30 to 120 and most preferably between 30 and 45, mg/day.

Brief Summary Text (142):

The preparation of metformin (dimethyldiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. The preparation of DRF2189 and of 5-{[4-(2-(2,3-dihydroindol-1-yl)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione is described in B. B. Lohray et al., J. Med. Chem. 1998, 41, 1619-1630; Examples 2d and 3g on pages 1627 and 1628. The preparation of 5-[3-(4-chlorophenyl)-2-propynyl]-5-phenylsulfonyl-thiazolidine-2,4-dione and the other compounds in which A is phenylethynyl mentioned herein can be carried out according to the methods described in J. Wrobel et al., J. Med. Chem. 1998, 41, 1084-1091.

Brief Summary Paragraph Table (3):

Treatment Group Treatment 1 60 mg nateglinide 2 250 mg metformin 3 60 mg nateglinide + 250 mg metformin 4 placebo only

Other Reference Publication (1):

"Huge Interest in Rosiglitazone and Pioglitazone", SCRIP, No. 2451, pp. 28-30 (1999).

Other Reference Publication (12):

Marre M et al., "Nateglinide Added to Metformin Offers Safe and Effective Treatment for Type 2 Diabetes", Diabetes, vol. 49, Supp. 1, p. 1517 (2000)--[2000:576788 SCISEARCH].

Other Reference Publication (16):

Hirschberg Y, "Improved Control of Mealtime Glucose Excursions With Coadministration of Nateglinide and Metformin", Diabetes Care, vol. 23, No. 3, pp. 349-353 (2000)--[Chemical Abstracts 132:329758p].

Other Reference Publication (17):

Horton E, "Nateglinide Alone and in Combination with Metformin Improves Glycemic Control by Reducing Mealtime Glucose Spikes in Type 2 Diabetes", Diabetologia, vol. 43, Supp. 1, p. A186 (2000)--[2000:456640 BIOSIS].

Other Reference Publication (19):

Horton ES et al., "Nateglinide Alone and in Combination with Metformin Improves Glycemic Control by Reducing Mealtime Glucose Levels in Type 2 Diabetes", Diabetes Care, vol. 23, No. 11, pp. 1660-1665 (2000)--[2000388708 EMBASE Alert].

Other Reference Publication (23):

Karara AH et al., "Lack of Pharmacokinetic Drug Interaction Between the Antidiabetic Agents A-4166 and Metformin", Pharm. Research, vol. 14, No. 11, Suppl., p. S557,--[xP-000997540].

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 14. Document ID: US 6011049 A

L2: Entry 14 of 14

File: USPT

Jan 4, 2000

DOCUMENT-IDENTIFIER: US 6011049 A  
TITLE: Combinations for diabetes

Brief Summary Text (7):

This invention provides a method of treating diabetes by administering to a subject in need of treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone, together with a biguanide antidiabetic agent such as metformin, or simply a glitazone together with a biguanide. The clinical data presented herein establishes the unexpected biological benefits achievable with these combinations.

Brief Summary Text (9):

Especially preferred sulfonylureas to be employed in the combinations of this invention are glyburide, gliguidone, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, glimepiride, phenbutamide, and tolcyclamide.

Brief Summary Text (24):

A typical biguanide is metformin. It typically is used clinically as a pharmaceutically acceptable salt, preferably the hydrochloride salt. A commercial form of metformin hydrochloride is available, and its chemical name is N,N-dimethylimidodicarbonimidic diamide hydrochloride. Metformin hydrochloride has the structural formula ##STR7## As used herein, "metformin" means the base compound as well as its pharmaceutically acceptable salts. Metformin is used clinically to manage NIDDM, particularly in patients who are not effectively treated with a sulfonylurea. While it is not chemically related to the sulfonylureas, it routinely is utilized in combination with a sulfonylurea, and has been shown to be synergistic in some cases. Other biguanides can also be used.

Drawing Description Text (2):

FIG. 1 Dose response of CS-045 (troglitazone), pioglitazone, and BRL-49653 (rosiglitazone) in causing reduction in red blood cell counts in female rats.

Drawing Description Text (3):

FIG. 2 Dose response of troglitazone, pioglitazone, and rosiglitazone in increases in brown adipose tissue in rats.

Drawing Description Text (4):

FIG. 3 Dose response of troglitazone, pioglitazone, and rosiglitazone in increasing heart weight (mass) in rats.

Drawing Description Text (5):

FIG. 4 Dose response (ED.sub.25) of troglitazone, pioglitazone, and rosiglitazone in causing a decrease in plasma glucose in KK mice.

Drawing Description Text (6):

FIG. 5 Dose response (ED.sub.25) of troglitazone, pioglitazone, and rosiglitazone in decreasing plasma glucose (%) in ZDF rats.

Drawing Description Text (7):

FIG. 6 Dose response of troglitazone, pioglitazone, and rosiglitazone in decreasing plasma glucose (%) in GK rats.

Drawing Description Text (8):

FIG. 7 Dose response of troglitazone, pioglitazone, and rosiglitazone in decreasing plasma glucose (%) in db/db mice.

Drawing Description Text (9):

FIG. 8 Change in fasting plasma glucose (FPG) (.-.SEM) during metformin and troglitazone monotherapy and during metformin and troglitazone combination therapy.

Drawing Description Text (10):

FIG. 9 Changes in FPG and post-prandial glucose (PPG) (.-.SEM) at 3 months of monotherapy of metformin and of troglitazone.

Drawing Description Text (11):

FIG. 10 (A) Mean percent change in endogenous glucose production (EGP) after 3 months of monotherapy of metformin and of troglitazone. (B) Mean percent change in glucose disposal rates (GDR) under hyperinsulinemic clamp conditions after 3 months of

monotherapy of metformin and of troglitazone.

Drawing Description Text (12):

FIG. 11 Changes in FPG and PPG after 3 months monotherapy of metformin and of troglitazone, and after an additional 3 months of combination therapy (metformin and troglitazone).

Drawing Description Text (13):

FIG. 12 Change in hemoglobin A1c (HbA.sub.1c) (.+-SEM) during 3 months of monotherapy of metformin and troglitazone and after an additional 3 months of combination therapy (metformin and troglitazone).

Detailed Description Text (3):

The dosage of each agent will vary depending upon the severity of the disease, the frequency of administration, the particular agents and combinations utilized, and other factors routinely considered by an attending medical practitioner. The sulfonylurea normally will be administered at a daily dose of from about 0.25 mg to about 500 mg, typically about 3 mg to about 250 mg. A typical dosage for glyburide, for example, will be about 10 to about 20 mg per day. The glitazones will normally be administered at doses from about 5 mg to about 2500 mg per day, and more typically from about 50 mg to about 1500 mg per day. A preferred glitazone is troglitazone, and it will be employed at doses from about 100 mg to about 1000 mg per day. A further preferred glitazone is rosiglitazone (BRL 49653), and it will be employed at doses of about 5 mg to about 10 mg per day. Another preferred glitazone is pioglitazone, and it will be employed at doses of about 50 mg to about 200 mg per day. Metformin hydrochloride will be administered at doses of about 300 mg to about 2000 mg per day. It is available commercially in tablets which contain 500 mg and 850 mg of active agent. These can be given up to two times a day or more.

Detailed Description Text (4):

Typical combinations to be employed according to this invention thus include troglitazone plus metformin, and troglitazone plus metformin plus a sulfonylurea such as glyburide. Another typical and preferred combination is rosiglitazone plus metformin, and rosiglitazone plus metformin plus a sulfonylurea such as glyburide. Still another preferred combination is pioglitazone plus metformin, and pioglitazone plus metformin plus a sulfonylurea such as glyburide. These combinations produce better than expected control of NIDDM.

Detailed Description Text (5):

The invention provides compositions of antidiabetic agents, for example, metformin and a glitazone, as well as metformin, a sulfonylurea and a glitazone, and a method of treating diabetes and controlling glycemic conditions comprising administering to a patient in need of treatment an effective amount of metformin and a glitazone, or metformin, a sulfonylurea and an effective amount of a glitazone. When the sulfonylurea and glitazone are formulated together, the compositions will contain about one to about 1000 parts by weight of sulfonylurea, and about 1000 to about one part by weight glitazone. For example, a typical composition of glyburide and troglitazone will contain about 12 mg of glyburide and about 500 mg of troglitazone. Such combination will be administered to an adult patient about once each day to achieve a desired glycemic control. Metformin can be combined directly with a glitazone such as troglitazone. Typical doses will be about 500 mg of metformin and about 300 to 600 mg of troglitazone. A typical three-way composition includes 12 mg of glyburide, 400 mg of troglitazone, and 500 mg of metformin.

Detailed Description Text (36):

Lipid changes observed in this study are consistent with results from prior studies. The favorable change in triglycerides, HDL, and FFA are contrasted by minimal increases in total cholesterol, LDL, Lp(a), and no changes in Apo (A1) and Apo (B). Collectively, these changes may be interpreted as having a potentially beneficial impact on atherogenic risk. It should be noted that patients with elevated triglycerides levels could potentially benefit from troglitazone treatment and provide synergism to the management of their dyslipidemia since elevated triglyceride levels are recognized as an independent risk factor for cardiovascular disease.

Detailed Description Text (47):

Another glitazone, namely BRL 49653 (now known as rosiglitazone, "RSG"), has undergone clinical evaluation and has demonstrated good efficacy in controlling glycemia in patients with type II diabetes. Rosiglitazone was evaluated in a multi-center, placebo-controlled trial. In this study, 493 patients with a fasting glucose between

7.8 mmol/L and 16.7 mmol/L were randomly assigned to treatment with placebo or rosiglitazone given at 4 mg or 8 mg per day. The rosiglitazone was administered as a twice-daily regimen for 26 weeks, following a 4-week placebo run-in period. The baseline demographic and metabolic characteristics of the patient population is given in Table 1.

Detailed Description Text (49):

The data presented in Table 2 demonstrate that rosiglitazone at 4 and 8 mg/day has a glucose-lowering effect compared to placebo-treated patients and to baseline. In a further analysis, the change from baseline in HbA.sub.1c in a subset of patients who had previously failed to be controlled on dietary therapy alone demonstrated a greater change from baseline in the patients treated with rosiglitazone. These results are shown in Table 3.

Detailed Description Text (50):

The data in Table 3 establish that rosiglitazone at 4 mg/day caused a 1.3% reduction in HbA.sub.1c relative to placebo-treated controls, and at 8 mg/day, caused a 1.38% reduction compared to placebo.

Detailed Description Text (51):

As noted above, rosiglitazone is a preferred glitazone to be combined with a sulfonylurea according to this invention. The sulfonylurea will be employed at a dose of about 0.25 mg to about 500 mg, typically from about 3 mg to about 250 mg. The rosiglitazone will be administered at a dose of about 5 to about 2500 mg per day, and more typically at a dose of about 5 mg to about 50 mg.

Detailed Description Text (57):

As noted above, the glitazones are a class of thiazolidinediones which have been shown to enhance hepatic and peripheral glucose uptake in animals, including humans, and are thus useful for treating diabetes mellitus. All of the glitazone compounds operate by the same mechanism within an animal system. Several studies have established the close similarity in biological activity of various glitazones from within the thiazolidinedione class. For example, troglitazone, pioglitazone, and rosiglitazone all cause a slight reduction in red blood cell counts when administered at various dosages to female rats (FIG. 1). Similarly, all three glitazones have about the same negligible effect on brown adipose tissue weight changes in rats (FIG. 2). Pioglitazone causes a slight increase in heart weight, whereas troglitazone has essentially no affect, and rosiglitazone causes an increase only at higher dose levels (FIG. 3). When tested in various mouse models, all three glitazones caused a substantial decrease in plasma glucose levels in a dose dependent fashion (FIGS. 4, 5, 6, and 7).

Detailed Description Text (59):

The glitazones can also be utilized in combination with a biguanide such as metformin, as well as in combination with a biguanide plus a sulfonylurea. Several clinical trials have established the unexpected biological efficacy that is achieved with a combination of troglitazone and metformin, as well as troglitazone, metformin, and glyburide.

Detailed Description Text (60):

In one clinical trial, patients were treated with monotherapy of metformin or troglitazone for 3 months, followed by combination therapy for 3 months. Twenty-nine patients diagnosed as having NIDDM were randomized. Fifteen subjects received metformin monotherapy, 1000 mg orally twice a day for 3 months. A group of 14 subjects were dosed orally with 400 mg of troglitazone once daily for 3 months. One patient randomized to troglitazone terminated participation after 2 weeks. One patient from each group completed the 3-month monotherapy phase, but withdrew prior to initiation of combination therapy. Two additional subjects, initially in the troglitazone monotherapy group, later withdrew from the combination phase before completion. The baseline characteristics of all subjects following the 3-month monotherapy phase are given in Table 5 below.

Detailed Description Text (62):

After the initial 3-month period of monotherapy, the remaining subjects were dosed with a combination of metformin and troglitazone (1000 mg metformin BID, 400 mg troglitazone QD) for an additional 3-month period.

Detailed Description Text (63):

At 3 months on monotherapy, both metformin and troglitazone caused a 20% decrease from baseline of FPG; 58 mg/dL and 54 mg/dL, respectively (FIG. 8). HbA.sub.1c levels did not change significantly with either drug. Mean post-prandial glucose decreased about

25% for both groups (metformin 87 mg/dL, troglitazone 83 mg/dL), as shown in FIG. 9. Post-prandial circulating insulin and C-peptide decreases were insignificantly different from baseline for both treatment groups. Following a 12-hour fasting period, all subjects were given a hyperinsulinemic-englycemic clamp assay. After the 3-month monotherapy treatment, EGP decreased from 108 to 87 mg/m.sup.2 /min (18%) in the metformin treated group (FIG. 10A), while troglitazone had no effect on EGP (FIG. 10B). In contrast, metformin caused less than 27% increase in glucose disposal rate (GDP) (240 to 272 mg/m.sup.2 /min) (FIG. 10B), whereas troglitazone caused a 97% increase (172 to 265 mg/m.sup.2 /min) (FIG. 10B).

#### Detailed Description Text (64):

When the study patients were given the combination of metformin and troglitazone for 3 months, dramatic and unexpected effects were observed. Fasting plasma glucose levels decreased an additional 18% (41 mg/dL) as shown in FIG. 8. Compared to baseline values, the mean decrease in FPG in all subjects over the entire 6-month treatment period was 98 mg/dL, or 35%. During the meal tolerance test, combination therapy caused an additional 21% decrease in plasma glucose (PG), or 54 mg/dL (FIG. 11). During the entire 6-month treatment period, total PG fell 41% or 140 mg/dL. HbA.sub.1c levels decreased 1.2% during the combination therapy (FIG. 12).

#### Detailed Description Text (65):

The foregoing study establishes that the combination of metformin and troglitazone causes a clinically significant and unexpected further lowering of both fasting and post-prandial glucose compared to either agent used alone. The combination provided by this invention thus provides further improvement in glucose control, without stimulation of insulin secretion.

#### Detailed Description Text (66):

Even more surprising are the clinical results observed when using a three-way combination of biguanide, sulfonylurea, and glitazone. A clinical trial was carried out assessing the effects of metformin, glyburide, and troglitazone when compared to a typical treatment regimen of glyburide and metformin. Two hundred NIDDM patients were enrolled in a double-blind, randomized, placebo-controlled multicenter study. All enrolled patients had compromised glycemic control and were currently treated with a sulfonylurea (comparable in dosage to at least 20 mg of glyburide) and at least 1500 mg of metformin daily. Of the 200 patients enrolled, 178 completed the 24-week trial. The study population consisted of 57% males, 43% females, with median age of 59. Patients had an average duration of NIDDM of 11.3 years. The population had an average weight of 85 kg (187 lbs), and BMI of 30.1 kg/m.sup.2. At the start of the trial, 101 patients received oral dosing of troglitazone (400 mg once daily), a sulfonylurea (SU), and metformin. The control group of 99 subjects received a sulfonylurea and metformin. The primary efficacy parameter measured was HbA.sub.1c. Secondary efficacy parameters were FSG, C-peptide, serum total insulin, BMI weight, triglycerides, total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Baseline glycemic levels at the start of the trial were: HbA.sub.1c : 9.7%; FPG: 234 mg/dL; circulating insulin level: 14.4 .mu.IN/mL; C-peptide: 3.4 ng/mL. The results of the clinical study after 24 weeks of treatment are presented in Table 6.

#### Detailed Description Text (67):

In the foregoing study, plasma glucose levels were reduced by 42 mg/dL at Week 8 in the group receiving the triple combination. This is a dramatically rapid reduction in FPG, showing the unexpectedly fast onset of action achieved with the triple combination, and the synergy associated with metformin, sulfonylurea, and glitazone. This represents good glycemic control in about one-half the time period normally observed in clinical settings using antidiabetic agents in monotherapy, or even using a combination of sulfonylurea and biguanide. Equally surprising was the dramatic reduction in endogenous insulin (19%) caused by the triple combination. Moreover, while the sulfonylurea/metformin combination had no effect on C-peptide levels, the triple combination of sulfonylurea/biguanide/glitazone caused a 7% reduction. Similarly, while the sulfonylurea/metformin treated group had an increase in triglycerides of 43 mg/dL, the sulfonylurea/glitazone/biguanide combination caused a reduction of 36 mg/dL.

#### Detailed Description Paragraph Table (2):

TABLE 2		Glucose-Lowering Effect of <u>Rosiglitazone</u>				
Placebo	RSG 4 mg/day	RSG 8 mg/day	(n = 158)	(n = 166)	(n = 169)	
				FPG (mmol/L)-Baseline	12.7	12.6
				12.2	Mean	A
				From		
Baseline	+1.05 (3.58)	-2.13 (2.91)	-3.00 (2.85)	(SD)	Comparison With	-- -3.20* -4.22*
Placebo	sup.a	95% CI	-- (-3.94, -2.48)	(-4.95, -3.49)	FPG (mg/dL)-Baseline	228.8
219.7	Mean	.increment.	From Baseline	8.9 (5.1)	-38.4 (4.1)	-54.0 (3.9) (SE) Comparison

With -- -57.7\* -76\* Placebo.sup.a 95% CI -- (-70.9, -44.6) (-89.2, -62.9) HbA.sub.1c (%) - Baseline 9.04 9.02 8.75 Mean .increment. From Baseline +0.92 (1.21) -0.28 (1.27) -0.56 (1.38) (SD) Comparison With -- -1.21\* -1.54\* Placebo.sup.a 95% CI -- (-1.52, -0.89) (-1.85, -1.22) a Adjusted mean difference  
\*p < 0.0001.

## Detailed Description Paragraph Table (3):

TABLE 3 Effect of Rosiglitazone in Diet-Failure Subset Placebo 4 mg/day 8 mg/day HbA.sub.1c (%) (Diet-Failure Subset) n= 45 44 45 Baseline 8.5 8.75 8.51 Mean .increment. From Baseline (SD) 0.47 (1.14) -0.83 (0.93) -0.91 (1.04)

## Detailed Description Paragraph Table (5):

TABLE 5 Baseline Characteristics of Subjects Who Completed the 3-Month Monotherapy Phase of the Trial Metformin Troglitazone Group (n = 15) Group (n = 13) p = Age (years) 51 (.-.3) 53 (.-.2) 0.32 (NS) Weight (kg) 99 (.-.4) 96 (.-.7) 0.68 (NS) BMI (kg/m.sup.2) 33.7 (.-.1.8) 34.0 (.-.2.3) 0.94 (NS) FPG (after "wash-out") 287 (.-.22) 275 (.-.21) 0.71 (NS) HbA.sub.1c (at screening) 9.8 (.-.0.5) 9.3 (.-.0.5) 0.42 (NS) Fasting insulin 24 (.-.3) 35 (.-.7) 0.16 (NS) Fasting C-peptide 1.9 (.-.0.1) 2.3 (.-.0.2) 0.13 (NS)

## Detailed Description Paragraph Table (6):

TABLE 6 Changes From Baseline at 24 Weeks SU + SU + Metformin + Adjusted Metformin Troglitazone Difference HbA.sub.1c +0.1 -1.3 (p < 0.001) -1.4 FPG +6 -42 (p < 0.001) -48 Circulating Insulin +1.4 -2.8 (p < 0.001) -3.3 C-peptide 0 -0.2 (p = 0.16) -0.2 Triglycerides +43 -36 (p = 0.07) -67 Total Cholesterol +6 +8 (p = 0.05) 4.8 HDL +1 +4 (p = 0.01) 3 LDL +2 +11 (p = 0.002) 9

## CLAIMS:

1. A composition comprising from about 3 mg to about 250 mg of a sulfonylurea antidiabetic agent, from about 5 mg to about 2500 mg of a glitazone antidiabetic agent selected from troglitazone, rosiglitazone and pioglitazone, and from about 300 mg to about 2000 mg of a biguanide antidiabetic agent, said amounts being synergistic in the treatment of non-insulin dependent diabetes mellitus.
3. A composition of claim 1 wherein the biguanide is metformin.
4. A synergistic composition comprising from about 100 mg to about 1000 mg of troglitazone, from about 3 mg to about 250 mg of glyburide, and from about 300 mg to about 2000 mg of metformin.
5. A synergistic composition comprising from about 5 mg to about 10 mg of rosiglitazone, from about 3 mg to about 250 mg of a sulfonylurea, and from about 300 mg to about 2000 mg of metformin.
6. A synergistic composition comprising from about 50 mg to about 200 mg of pioglitazone, from about 3 mg to about 250 mg of a sulfonylurea, and from about 300 mg to about 2000 mg of metformin.
7. A method of treating diabetes by administering to a patient in need of treatment from about 3 mg to about 250 mg of a sulfonylurea antidiabetic agent in combination with from about 5 mg to about 2500 mg of a glitazone antidiabetic agent selected from troglitazone, rosiglitazone and pioglitazone and from about 300 mg to about 2000 mg of a biguanide antidiabetic agent, wherein said amounts are synergistic for the treatment of non-insulin dependent diabetes mellitus.
9. A method according to claim 8 wherein the glitazone antidiabetic agent is selected from troglitazone, pioglitazone, and rosiglitazone.
10. A method according to claim 8 wherein the biguanide is metformin.
12. A method according to claim 10 wherein the glitazone is rosiglitazone.
14. A method of treating diabetes by administering to a patient in need of treatment from about 5 mg to about 10 mg of rosiglitazone together with from about 300 mg to about 2000 mg of metformin and from about 3 mg to about 250 mg of a sulfonylurea,

wherein said amounts are synergistic for the treatment of non-insulin dependent diabetes mellitus.

15. A method of treating diabetes by administering to a patient in need of treatment from about 100 mg to about 1000 mg of troglitazone together with from about 300 mg to about 2000 mg of metformin and from about 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment of non-insulin dependent diabetes mellitus.

16. A method of treating diabetes by administering to a patient in need of treatment from about 50 mg to about 200 mg of pioglitazone together with from about 300 mg to about 2000 mg of metformin and from about 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment of non-insulin dependent diabetes mellitus.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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Term	Documents
ROSIGLITAZONE	526
ROSIGLITAZONES	0
METFORMIN	1157
METFORMINS	0
GLIMEPIRIDE	393
GLIMEPIRIDES	0
SYNERGISM	6265
SYNERGISMS	105
(GLIMEPIRIDE AND ROSIGLITAZONE AND METFORMIN AND SYNERGISM).USPT,PGPB.	14
((((ROSIGLITAZONE METFORMIN GLIMEPIRIDE ) SYNERGISM)).USPT,PGPB.	14

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glycogen phosphorylase inhibitors for treatment of type 2 diabetes)

L9 ANSWER 14 OF 27 USPATFULL on STN  
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TI 2,1-Oxazoline and 1,2-pyrazoline-based inhibitors of dipeptidyl  
peptidase IV and method  
IN Sulsky, Richard B., West Trenton, NJ, UNITED STATES  
Robl, Jeffrey A., Newtown, PA, UNITED STATES  
PI US 2002183367 A1 20021205  
US 6573287 B2 20030603  
AI US 2002-107279 A1 20020326 (10)  
PRAI US 2001-283438P 20010412 (60)  
DT Utility  
FS APPLICATION  
LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O  
BOX 4000, PRINCETON, NJ, 08543-4000  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1448  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Dipeptidyl peptidase IV (DP 4) inhibiting compounds are provided having  
the formula ##STR1##

where n is 0 or 1; X is H or CN;

Y is N, NH or O;

Z is CH.sub.2 when Y is O or N--H, with Y--Z forming a single bond, and  
Z is CH when Y is N, with Y--Z forming a double bond;

and wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described  
herein.

A method is also provided for treating diabetes and related diseases,  
especially Type II diabetes, and other diseases as set out herein,  
employing such DP 4 inhibitor or a combination of such DP 4 inhibitor  
and one or more of another antidiabetic agent such as **metformin**  
, glyburide, troglitazone, pioglitazone, rosiglitazone and/or insulin  
and/or one or more of a hypolipidemic agent and/or anti-obesity agent  
and/or other therapeutic agent.

AB . . . 4 inhibitor or a combination of such DP 4 inhibitor and one or  
more of another antidiabetic agent such as **metformin**,  
glyburide, troglitazone, pioglitazone, rosiglitazone and/or insulin  
and/or one or more of a hypolipidemic agent and/or anti-obesity agent  
and/or other therapeutic. . .

SUMM [0073] The other antidiabetic agent may be an oral antihyperglycemic  
agent preferably a biguanide such as **metformin** or phenformin  
or salts thereof, preferably **metformin** HCl.

SUMM [0075] The other antidiabetic agent may also preferably be a sulfonyl  
urea such as glyburide (also known as glibenclamide),  
**glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide,  
gliclazide or chlorpropamide, other known sulfonylureas or other  
antihyperglycemic agents which act on. . .

SUMM [0083] Where present, **metformin**, the sulfonyl ureas, such as  
glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide  
and gliclazide and the glucosidase inhibitors acarbose or miglitol or  
insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0084] Where present, **metformin** or salt thereof may be  
employed in amounts within the range from about 500 to about 2000 mg per  
day. . .

CLM What is claimed is:

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15. The combination as defined in claim 14 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipyrizide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, . . .

IT 94-20-2, Chlorpropamide 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 21187-98-4, Gliclazide 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 93479-97-1, Glimepiride 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 135062-02-1, Repaglinide 141732-76-5, Exendin-4 141758-74-9, AC2993 170861-63-9, JTT-501 176435-10-2, LY315902 196808-45-4 199914-96-0, YM-440 204656-20-2, NN 2211 213252-19-8, KRP297 244081-42-3, AJ9677 335149-06-9, NN-2344 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544 430433-17-3, Glipyrizide 430433-39-9, Isaglitazone 473266-48-7, LY 307161  
(antidiabetic agent; prepn. of oxazoline and pyrazoline-based inhibitors of dipeptidyl peptidase IV).

L9 ANSWER 15 OF 27 USPATFULL on STN

AN 2002:290588 USPATFULL

TI Biphasic controlled release delivery system for high solubility pharmaceuticals and method

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PI US 6475521 B1 20021105

AI US 1999-398107 19990916 (9)

RLI Continuation-in-part of Ser. No. US 1998-44446, filed on 19 Mar 1998, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Spear, James M.

LREP Davis, Stephen B.

CLMN Number of Claims: 50

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 1674

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic **metformin** HCl salt, is provided which provides a dosage form that has prolonged gastric residence so that a dosing regimen of at least one gram **metformin**, once daily, may be achieved while providing effective control of plasma glucose. The delivery system includes (1) an inner solid particulate phase formed of substantially uniform granules containing a pharmaceutical having a high water solubility, and one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, and (2) an outer solid continuous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout, the outer solid continuous phase including one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, which may be compressed into tablets or filled into capsules. Methods for forming the so-described biphasic controlled release delivery system and using such biphasic controlled release delivery system for treating diabetes are also provided.

AB A biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic **metformin** HCl salt, is provided which provides a dosage form that has prolonged gastric residence so that a dosing regimen of at least one gram **metformin**, once daily, may be achieved while providing effective control of plasma glucose. The delivery system includes (1) an inner solid. . .

SUMM The present invention relates to a new dosage form for highly water soluble medicaments, such as the antidiabetic **metformin**, which provides for extended release of the drug and also for prolonged gastric residence, so that a dosing regimen of at least one gram **metformin** once daily, may be achieved while providing effective control of plasma glucose, and to a method for treating diabetes employing. . .

SUMM **Metformin** is an antihyperglycemic agent of the biguanide class used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It is. . .

SUMM **Metformin** hydrochloride has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the. . . a formulation. These two difficulties are further compounded by the high unit dose, 500 mg per tablet, usually required for **metformin** hydrochloride (1997-PDR).

SUMM Studies by Vidon et al (1) strongly suggest that there is permeability limited absorption of **metformin**. Perfusing drug into the jejunum via an intubation technique showed a 2.5 fold greater area under the plasma concentration-time profile. . .

SUMM Improvements in the therapeutic regimes employing **metformin** might be achieved by a dosage form that allows a reduction in dosing frequency, providing patient convenience that would probably improve compliance. Conventional extended release formulations have been demonstrated to invariably compromise the availability of **metformin** (2), (2A), and (2B). This is probably because the dosage form carries a significant proportion of the drug content remaining. . .

SUMM Maintained or even improved bioavailability from an extended release dosage form that releases **metformin** at a rate likely to provide the desired plasma levels of drug for an extended time period might, however, be. . . normal transit time for solid materials. That this principle might work in practice was demonstrated in an in-house study where **metformin** was co-administered with propantheline, an agent that reduces gastrointestinal motility. Compared with giving **metformin** alone, the combination provided an increased AUC, a delayed tmax and an extended time period over which therapeutically beneficial plasma. . .

SUMM Giving a drug such as **metformin** for the treatment of diabetes with a further drug, such as propantheline, not used for the treatment of diabetes and. . . residence time in the upper GI tract, has many disadvantages although it is likely to allow effective extended delivery of **metformin** to an optimal absorption site. The co-administered drug may have other undesirable pharmacological effects or side effects deleterious to the. . .

SUMM In the case of **metformin**, it is desirable to provide a dosage form that allows extended delivery of the drug and has a prolonged gastric. . . manufactured on a commercial scale. The prolonged gastric residence time is required due to the window of absorption seen with **metformin**.

SUMM Another problem for extended delivery of **metformin** is its very high water solubility. High levels of polymer would be needed if many prior art approaches to provide. . .

SUMM . . . novel way has been found of formulating drug with high water solubility and a limited window of absorption such as **metformin** or a salt thereof which has a window of absorption in the upper

gastrointestinal tract, to provide a dosage form. . .

SUMM In the case of **metformin**, the formulation of the invention allows a patient a dosing regimen of at least one gram **metformin**, once-daily, preferably from about 1 to about 3 grams, once daily, in the form of one or more tablets and/or one or more capsules, while providing effective control of plasma glucose. The **metformin** formulations of the invention may be administered once daily at the above dosages to effectively treat diabetes while avoiding problems which may be associated with high plasma **metformin** levels as may be encountered with conventional **metformin** formulations, while providing optimum therapeutic control.

SUMM . . . particulate phase in the form of individual granules or particles containing (a) drug which has a high water solubility, preferably, **metformin** or a salt thereof, and a limited window of absorption (such as in the upper gastrointestinal tract), and (b) an.

SUMM The biphasic controlled release formulation of the invention is particularly adapted for delivery of high water soluble drugs, such as **metformin** and pharmaceutically acceptable salts thereof, in controlled and extended manner without significant initial burst of drug, and wherein release of. . .

SUMM The antidiabetic pharmaceutical employed is preferably a biguanide, preferably **metformin** or a pharmaceutically acceptable salt thereof such as the hydrochloride, hydrobromide, fumarate, succinate, p-chlorophenoxy acetate or embonate, all of which are collectively referred to as **metformin**. The fumarate and succinate salts are preferably the **metformin** (2:1) fumarate, and the **metformin** (2:1) succinate disclosed in U.S. application Ser. No. 09/262,526 filed Mar. 4, 1999. **Metformin** hydrochloride salt is preferred.

SUMM . . . method is provided for lowering insulin resistance or treating diabetes wherein the biphasic controlled release formulation of the invention contains **metformin** and is administered in a dosing regimen of at least one gram **metformin**, once daily, preferably from about 1 to about 3 grams, once daily, to a patient in need of treatment.

SUMM

% by Weight of Inner

A. Inner Solid Particulate Phase Solid Particulate Phase

- (1) **Metformin** HCl (or other 55 to 98 salt such as succinate or fumarate)
- (2) Polymer or Hydrophobic 5 to 95

SUMM The preferred drug (having high water solubility) for use herein is **metformin** or pharmaceutically acceptable salts thereof, including the hydrochloride salt and dibasic salts such as **metformin** (2:1) fumarate and **metformin** (2:1) succinate as described in pending U.S. application Ser. No. 09/262,526 filed Mar. 4, 1999, now U.S. Pat. No. 6,031,004, . . .

SUMM Most preferred are the **metformin** hydrochloride salt, **metformin** (2:1) succinate salt, and **metformin** (2:1) fumarate salt.

SUMM Where desired, **metformin** or a salt thereof may be used in combination with another antihyperglycemic agent and/or a hypolipidemic agent which may be. . . orally in the same dosage form in accordance with the invention, a separate oral dosage form or by injection. The **metformin** or salt thereof will be employed in a weight ratio to the other antihyperglycemic agent and/or hypolipidemic agent within the. . .

SUMM It is believed that the use of the **metformin** or salt thereof in combination with another anti-hyperglycemic agent produces antihyperglycemic results greater than that possible from each of these.

SUMM . . . diabetes (NIDDM) and/or type 1 diabetes (IDDM) wherein a therapeutically effective amount of the biphasic formulation of the invention containing **metformin** or a salt thereof, optionally in combination with another antihyperglycemic agent and/or a hypolipidemic agent, is administered to a patient. . .

SUMM . . . other antihyperglycemic agent may be an oral antihyperglycemic agent preferably a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM The **metformin** or salt thereof will be employed in a weight ratio to the sulfonyl urea in the range from about 300:1. . .

SUMM The **metformin** salt thereof will be employed in a weight ratio to the glucosidase inhibitor within the range from about 300:1 to. . .

SUMM The **metformin** or salt thereof may be employed in combination with a thiazolidinedione oral anti-diabetic agent (which has an insulin sensitivity effect. . .

SUMM The **metformin** or salt thereof will be employed in a weight ratio to the thiazolidinedione in an amount within the range from. . .

SUMM The **metformin** or salt thereof may also be employed in combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like. . .

SUMM Where present, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol may be employed in formulations as described. . .

SUMM The hypolipidemic agent which may be optionally employed in combination with **metformin** or a salt thereof may include MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors,. . .

SUMM The **metformin** or salt thereof and the hypolipidemic agent may be employed together in the same oral dosage form or in separate. . .

SUMM Preferably, the water-soluble drug is **metformin** or salt thereof as described above.

SUMM . . . the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms of formulation containing **metformin** or salt thereof (whether by itself or with another antihyperglycemic agent and/or a hypolipidemic agent) described above may be administered in amounts as described for **metformin** hydrochloride (Bristol-Myers Squibb Company's Glucophage.RTM.) as set out in the Physician's Desk Reference.

SUMM The combination of the **metformin** or salt thereof and the other antihyperglycemic agent and/or hypolipidemic agent may be formulated separately or, where possible, in a. . .

SUMM As indicated, the preferred highly water-soluble drug will be **metformin** or a salt thereof, which will be employed in a dosage range from about 2 to about 43 mg/kg, preferably. . .

SUMM Where **metformin** is to be administered once daily, **metformin** will be employed in an amount of at least one gram, preferably from about one to about 3 grams and. . .

SUMM A mixture of medicament (preferably **metformin** HCl) and hydrophilic polymer and/or hydrophobic polymer and/or other hydrophobic material are dispersed/dissolved in a suitable solvent such as water. . .

SUMM Useful **metformin** formulations of the invention show the following drug release characteristic when tested in vitro.

SUMM In addition, in accordance with the present invention, the controlled release **metformin** formulation of the invention (relative to

the rapid-release marketed Glucophage.RTM. tablets) reduces maximum attained plasma-**metformin** concentration (Cmax) by at least about 15% (preferably from about 15 to about 30%), and increases time to reach maximum **metformin** plasma concentration (Tmax) by at least about 30% (preferably from about 30 to about 100%), while having an insignificant effect on area under the plasma-**metformin** concentration time curve (AUC) and % urinary recovery (UR) of the dose of **metformin**. Thus, the controlled-release **metformin** formulation of the invention can be employed for once daily dosing of **metformin** in the treatment of diabetes.

DETD Biphasic **Metformin** HCl Formulation

DETD . . . ethylcellulose N10 NF was dissolved/dispersed in 100 ml of 95% ethanol. This dispersion was gradually added to 500 g of **metformin** hydrochloride in a planetary mixer to produce a uniform damp granulation. The granulation was dried at 55.degree. C. for one hour and passed through a 0.8 mm aperture screen to break down agglomerates. The **metformin**-ethylcellulose granules (541 g) were blended with 351.5 g of hydroxypropylmethylcellulose 2208 USP (100,000 cps grade), 10 g of hydroxypropylmethylcellulose 2910. . . Finally this mix was lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500 mg **metformin** hydrochloride. When subjected to in vitro drug release testing, the following results were obtained.

DETD

Time (hours) % **metformin** released

1 38.1  
2 56.3  
3 69.5  
4 79.7  
5 87.4  
6 93.1  
7 97.7  
8 100

DETD Biphasic **Metformin** HCl Formulation

DETD 51 g of sodium carboxymethylcellulose (Blanose 7HF) was mixed with 500 g of **metformin** hydrochloride and granulated with 95% ethanol in a small planetary mixer. The damp granulation was passed through a 2 mm. . . minutes. This blend was lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500 mg **metformin** hydrochloride. When the tablets were subjected to in vitro release testing the following results were obtained.

DETD

Time (hours) % **metformin** released

1 35.3  
2 51.4  
3 62.6  
4 70.7  
5 76.7  
6 82.1  
7 85.3  
8 88.5  
10 92.6

DETD Biphasic **Metformin** HCl Formulation

DETD . . . was lubricated by mixing with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 0.5 g of **metformin** hydrochloride. When tested for in vitro release of

**metformin** the following results were obtained.

DETD

Time (hours) % **metformin** released

1 33.1  
2 47.6  
3 57.5  
4 65.1  
6 76.5  
8 84.3  
10 88.6

DETD Biphasic **Metformin** HCl Formulation

DETD 200 g of glycerol monostearate was heated to 70.degree. C. in a high shear mixer bowl and 199 g of **metformin** hydrochloride was added and the mixer operated with impeller at 90 rpm and chopper at 215 rpm for 5 minutes. A further 796 g of **metformin** hydrochloride was added gradually with continued mixing, maintaining the granulation at 70.degree. C. and with an increase in chopper speed. . .

DETD . . . was lubricated by blending with 1% w/w magnesium stearate and then compressed into capsule shaped tablets each containing 500 mg **metformin** hydrochloride. When tested for in vitro release of **metformin**, the following results were obtained.

DETD

Time (hours) % **metformin** released

1 32.4  
2 45.7  
3 55.8  
4 63.7  
5 70.3  
6 75.7  
8 83.3  
10 88.6

DETD Biphasic **Metformin** HCl Formulation

DETD Tablets containing 500 mg **metformin** hydrochloride prepared according to Example 3 or Glucophage brand (or rapid release) **metformin** hydrochloride 500 mg tablets was dosed (2.times.500 mg tablets) to 24 patients immediately after dinner. Blood samples were taken at. . . 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24 hours and analyzed for **metformin**. The mean plasma profile demonstrated useful modification of drug release in vivo relative to the immediate release formulation and with no impact on bioavailability in contrast to other **metformin** extended release formulations reported in the literature.

DETD . . . a day tablet formulation of the invention (relative to the rapid release Glucophage.RTM. tablet), the time required to reach maximum **metformin** plasma concentration (Tmax) is increased by an average of about 40%, and the maximum attained plasma **metformin** concentration (Cmax) is reduced by an average of about 20%, yet the area under plasma-**metformin** concentration time curve (AUC) and the % urinary recovery (UR) of the dose of **metformin** are not significantly different from that found with rapid-release Glucophage.RTM.. This means that overall patient exposure to **metformin** (in both the Example 3 formulation and the Glucophage.RTM.) is equivalent.

DETD . . . tablet formulation of the invention indicate that the Example 3 tablet formulation can be employed for once daily dosing of **metformin** in the treatment of diabetes.

DETD The new formulations of the invention thus represent a significant advance in the once-a-day administration of **metformin** hydrochloride to humans in the treatment of diabetes.

DETD Preparation of **Metformin** (2:1) Fumarate

DETD **Metformin** base (8.71 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H.sub.2O [5:1]. With stirring, a. . . one hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to afford the **metformin** (2:1) fumarate salt as a free-flowing white crystalline solid in 72 M % yield and melting point of 247-249.degree. C.

DETD The resulting **metformin** (2:1) fumarate salt had a solubility in water (mg/ml) of 140, a hygroscopicity measured at 95% relative humidity/25.degree. C. of. . .

DETD The so-formed **metformin** salt is used to prepare a biphasic controlled release formulation employing the procedure of Example 3.

DETD Preparation of **Metformin** (2:1) Succinate

DETD **Metformin** base (8.95 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H.sub.2O [5:1]. With stirring, a. . . an hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to form the **metformin** (2:1) succinate salt as a free flowing white crystalline solid in 89 M% yield and melting point of 246-247.degree. C.

DETD The resulting **metformin** (2:1) succinate salt had a solubility in water (mg/ml) of 95, a hygroscopicity measured at 95% relative humidity/25.degree. C. of. . .

DETD The so-formed **metformin** salt is used to prepare a biphasic controlled release formulation employing the procedure of Example 3.

DETD The **metformin** formulations described in the aforesaid Examples may be administered once daily as described above, in one, two or more tablets. . .

DETD 2A. Noel, D. S. (1980), Kinetic study of normal and sustained release dosage forms of **metformin** in normal subjects, Journal of International Biomedical Information and Data, 1980, pp. 9 to 20.

DETD 2B. Karttunen et al (1983), The pharmacokinetics of **metformin** : a comparison of the properties of a rapid-release and a sustained-release preparation, Int. J. Clin. Pharmacology, Therapy and Toxicology, . . .

CLM What is claimed is:

. . . embedded, the particles of the inner solid particulate phase comprising (a) a pharmaceutical having a high water solubility selected from **metformin** or a pharmaceutically acceptable salt thereof; and (b) an extended release material, and the outer solid continuous phase comprising an. . .

4. The pharmaceutical formulation as defined in claim 1 wherein the pharmaceutical is **metformin** hydrochloride.

8. The pharmaceutical formulation as defined in claim 1 which when ingested by a human reduces maximum attained plasma-**metformin** concentration (Cmax) by at least about 15% (relative to marketed rapid-release **metformin** formulations), and increases time to reach maximum **metformin**-plasma concentration (Tmax) by at least about 30% (relative to marketed rapid-release **metformin** formulations), while having an insignificant effect on area under the plasma-**metformin** concentration time curve (AUC) and % urinary recovery (UR) of the dose of **metformin** (relative to marketed rapid-release **metformin** formulations).

9. The pharmaceutical formulation as defined in claim 1 comprising **metformin** in a therapeutically effective amount which allows a patient a dosing regimen of at least one gram **metformin**, or a pharmaceutically acceptable salt thereof, once daily, while providing

effective control of plasma glucose.

13. The pharmaceutical formulation as defined in claim 9 which when ingested by a human reduces maximum attained plasma-**metformin** concentration (Cmax) by at least about 15% (relative to marketed rapid-release **metformin** formulations), and increases time to reach maximum **metformin**-plasma concentration (Tmax) by at least about 30% (relative to marketed rapid-release **metformin** formulations), while having an insignificant effect on area under the plasma-**metformin** concentration time curve (AUC) and % urinary recovery (UR) of the dose of **metformin** (relative to marketed rapid-release **metformin** formulations).

14. The pharmaceutical formulation as defined in claim 1 wherein the **metformin** is **metformin** (2:1) fumarate.

21. The pharmaceutical formulation as defined in claim 1 wherein the inner solid particulate phase comprises **metformin**, **metformin** hydrochloride, **metformin** succinate (2:1) salt or **metformin** fumarate (2:1) salt, and ethyl cellulose and/or sodium carboxymethyl cellulose and/or glycerylmonostearate and the outer solid continuous phase comprises hydroxypropylmethylcellulose.

27. The pharmaceutical formulation as defined in claim 22 wherein the **metformin** is present in a weight ratio to the other antihyperglycemic agent or hypolipidemic agent within the range from about 0.01:1.

. . . form of a biphasic controlled release delivery system, which comprises forming an inner solid particulate phase comprising individual particles comprising **metformin** or a pharmaceutically acceptable salt thereof and an extended release material and mixing the individual particles forming the inner solid.

. . . of the inner solid particulate phase are dispersed and embedded, the particles of the inner solid particulate phase comprising (a) **metformin** or a pharmaceutically acceptable salt thereof; and (b) an extended release material, and the outer solid continuous phase comprising an.

. . . pharmaceutical formulation as defined in claim 30 which is a biphasic heterogeneous controlled release formulation which is designed to release **metformin** from the particles forming the inner solid particulate phase through the outer solid continuous phase into the upper gastrointestinal tract.

32. The pharmaceutical formulation as defined in claim 30 wherein the **metformin** is **metformin** hydrochloride.

37. The pharmaceutical formulation as defined in claim 30 wherein the **metformin** is **metformin** (2:1) fumarate.

39. The pharmaceutical formulation as defined in claim 30 wherein the **metformin** is present in the inner solid particulate phase in an amount within the range from about 10 to about 98%.

44. The pharmaceutical formulation as defined in claim 30 wherein the inner solid particulate phase comprises **metformin**, **metformin** hydrochloride, **metformin** succinate (2:1) salt or **metformin** fumarate (2:1) salt, and ethyl cellulose and/or sodium carboxymethyl cellulose and/or glycerylmonostearate and the outer solid continuous phase comprises hydroxypropylmethylcellulose.

50. The pharmaceutical formulation as defined in claim 30 which when ingested by a human reduces maximum attained plasma-**metformin** concentration (Cmax) by at least about 15% (relative to marketed rapid-release **metformin** formulations), and increases time to

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right truncation  
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Right Truncation available  
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September 2003  
NEWS 32 AUG 15 PCTGEN: one FREE connect hour, per account, in  
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September 2003  
NEWS 35 AUG 18 Data available for download as a PDF in RDISCLOSURE  
NEWS 36 AUG 18 Simultaneous left and right truncation added to PASCAL  
NEWS 37 AUG 18 FROSTI and KOSMET enhanced with Simultaneous Left and Right  
Truncation  
NEWS 38 AUG 18 Simultaneous left and right truncation added to ANABSTR

641426

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
 MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
 AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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DICTIONARY FILE UPDATES: 4 SEP 2003 HIGHEST RN 579436-73-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

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=> file registry  
COST IN U.S. DOLLARS  
  
FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
1.20	1.62

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Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 4 SEP 2003 HIGHEST RN 579436-73-0  
DICTIONARY FILE UPDATES: 4 SEP 2003 HIGHEST RN 579436-73-0

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

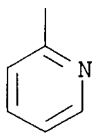
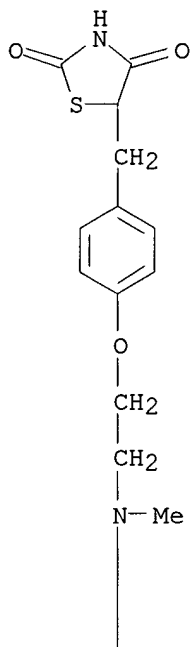
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s rosiglitazone/cn  
L1 1 ROSIGLITAZONE/CN

=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN  
RN 122320-73-4 REGISTRY  
CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]met  
hyl]- (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione  
CN BRL 49653  
CN **Rosiglitazone**  
FS 3D CONCORD  
MF C18 H19 N3 O3 S  
CI COM  
SR CA  
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS,  
BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
CIN, CSCHM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES,  
EMBASE, IPA, MEDLINE, MRCK\*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN,  
USPAT2, USPATFULL  
(\*File contains numerically searchable property data)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

645 REFERENCES IN FILE CA (1937 TO DATE)  
 6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 650 REFERENCES IN FILE CAPLUS (1937 TO DATE)

=> file uspatfull  
 COST IN U.S. DOLLARS  
 FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
6.70	8.32

FILE 'USPATFULL' ENTERED AT 13:42:42 ON 05 SEP 2003  
 CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Sep 2003 (20030904/PD)  
 FILE LAST UPDATED: 4 Sep 2003 (20030904/ED)  
 HIGHEST GRANTED PATENT NUMBER: US6615408  
 HIGHEST APPLICATION PUBLICATION NUMBER: US2003167547  
 CA INDEXING IS CURRENT THROUGH 4 Sep 2003 (20030904/UPCA)  
 ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Sep 2003 (20030904/PD)  
 REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2003  
 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2003

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>>> USPAT2 is now available.  USPATFULL contains full text of the    <<<
>>> original, i.e., the earliest published granted patents or        <<<
>>> applications.  USPAT2 contains full text of the latest US       <<<
>>> publications, starting in 2001, for the inventions covered in    <<<
>>> USPATFULL.  A USPATFULL record contains not only the original   <<<
>>> published document but also a list of any subsequent            <<<
>>> publications.  The publication number, patent kind code, and    <<<
>>> publication date for all the US publications for an invention   <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.                                                         <<<

>>> USPATFULL and USPAT2 can be accessed and searched together      <<<
>>> through the new cluster USPATALL.  Type FILE USPATALL to        <<<
>>> enter this cluster.                                              <<<
>>>                                                                    <<<
>>> Use USPATALL when searching terms such as patent assignees,     <<<
>>> classifications, or claims, that may potentially change from    <<<
>>> the earliest to the latest publication.                          <<<

```

This file contains CAS Registry Numbers for easy and accurate substance identification.

```

=> s 122320-73-4/rn
L2      156 122320-73-4/RN

```

```

=> s 12 and 4mg
      419 4MG
L3      0 L2 AND 4MG

```

```

=> s 13 and 12 mg
      3036031 12
      319828 MG
      10087 12 MG
      (12(W)MG)
L4      0 L3 AND 12 MG

```

```

=> s 12 and diabetes
      27560 DIABETES
L5      130 L2 AND DIABETES

```

```

=> s 12 and synerg?
      51450 SYNERGI?
L6      32 L2 AND SYNERGI?

```

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=> d 16 1-32 bib, ab

```

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L6  ANSWER 1 OF 32  USPATFULL on STN
AN  2003:207969  USPATFULL
TI  Methods and pharmaceutical compositions for inhibiting tumor cell growth
IN  Spiegelman, Bruce M., Waban, MA, UNITED STATES
    Mueller, Elisabetta, Boston, MA, UNITED STATES
    Sarraf, Pasha, Boston, MA, UNITED STATES
    Altiok, Soner, Cambridge, MA, UNITED STATES
    Tontono, Peter, Los Angeles, CA, UNITED STATES
    Singer, Samuel, Brookline, MA, UNITED STATES
PI  US 2003144330      A1  20030731
AI  US 2002-324744      A1  20021219 (10)
RLI Continuation of Ser. No. US 1997-923346, filed on 4 Sep 1997, GRANTED,
    Pat. No. US 6552055 Continuation of Ser. No. US 1996-766553, filed on 11
    Dec 1996, ABANDONED
DT  Utility

```

FS APPLICATION  
LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109  
CLMN Number of Claims: 48  
ECL Exemplary Claim: 1  
DRWN 16 Drawing Page(s)  
LN.CNT 2299

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is based on the finding that activation of PPAR.gamma. plays a key role in inducing growth arrest and differentiation of certain actively proliferating cells. We show that administration of PPAR.gamma. agonists, such as thiazolidinedione ligands (TZDs), is effective both in vitro and in vivo at inhibiting the proliferation of such cells.

L6 ANSWER 2 OF 32 USPATFULL on STN

AN 2003:201447 USPATFULL

TI Combinations comprising dipeptidylpeptidase-iv inhibitor

IN Balkan, Bork, Madison, CT, UNITED STATES

Hughes, Thomas Edward, Somerville, NJ, UNITED STATES

Holmes, David Grenville, Binningen, SWITZERLAND

Villhauer, Edwin Bernard, Morristown, NJ, UNITED STATES

PI US 2003139434 A1 20030724

AI US 2002-181169 A1 20021010 (10)

WO 2001-EP590 20010119

PRAI US 2000-9489234 20000121

US 2000-9619262 20000719

DT Utility

FS APPLICATION

LREP THOMAS HOXIE, NOVARTIS, PATENT AND TRADEMARK DEPARTMENT, ONE HEALTH

PLAZA 430/2, EAST HANOVER, NJ, 07936-1080

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1581

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, .alpha.-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and .alpha..sub.2-adrenergic antagonists, for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

L6 ANSWER 3 OF 32 USPATFULL on STN

AN 2003:166531 USPATFULL

TI Combination of organic compounds

IN Webb, Randy Lee, Flemington, NJ, UNITED STATES

PI US 2003114389 A1 20030619  
 AI US 2002-290651 A1 20021108 (10)  
 PRAI US 2001-350708P 20011113 (60)  
 DT Utility  
 FS APPLICATION  
 LREP THOMAS HOXIE, NOVARTIS, CORPORATE INTELLECTUAL PROPERTY, ONE HEALTH  
 PLAZA 430/2, EAST HANOVER, NJ, 07936-1080  
 CLMN Number of Claims: 7  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 601  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to a combination, such as a combined preparation  
 or pharmaceutical composition, respectively, comprising the renin  
 inhibitor of formula (I) or a pharmaceutically acceptable salt thereof  
 and at least one antidiabetic agent.

L6 ANSWER 4 OF 32 USPATFULL on STN  
 AN 2003:134661 USPATFULL  
 TI Treatment of diabetes with thiazolidinedione, insulin secretagogue and  
 alpha glucosidase inhibitor  
 IN Buckingham, Robin Edwin, Welwyn Garden City, UNITED KINGDOM  
 Smith, Stephen Alistair, Bramfield, UNITED KINGDOM  
 PA SmithKline Beecham p.l.c. (non-U.S. corporation)  
 PI US 2003092750 A1 20030515  
 AI US 2002-322982 A1 20021218 (10)  
 RLI Continuation of Ser. No. US 2001-989572, filed on 20 Nov 2001, ABANDONED  
 Continuation of Ser. No. US 1999-445908, filed on 15 Dec 1999, ABANDONED  
 A 371 of International Ser. No. WO 1998-GB2112, filed on 16 Jul 1998,  
 UNKNOWN  
 PRAI GB 1997-15298 19970718  
 DT Utility  
 FS APPLICATION  
 LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box  
 1539, King of Prussia, PA, 19406-0939  
 CLMN Number of Claims: 22  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 493  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB A method for the treatment of diabetes mellitus and conditions  
 associated with diabetes mellitus in a mammal, which method comprises  
 administering an effective non-toxic and pharmaceutically acceptable  
 amount of an insulin sensitizer, an insulin secretagogue and an alpha  
 glucosidase inhibitor antihyperglycaemic agent, to a mammal in need  
 thereof; and composition for use in such method.

L6 ANSWER 5 OF 32 USPATFULL on STN  
 AN 2003:123367 USPATFULL  
 TI Method of treating metabolic disorders especially diabetes, or a disease  
 or condition associated with diabetes  
 IN Gatlin, Marjorie Regan, Hoboken, NJ, United States  
 Ball, Michele Ann, Morris Plains, NJ, United States  
 Mannion, Richard Owen, Mount Arlington, NJ, United States  
 Karnachi, Anees Abdulquadar, Hillsborough, NJ, United States  
 Guitard, Christiane, Hegenheim, FRANCE  
 Allison, Malcolm, Basel, SWITZERLAND  
 PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)  
 PI US 6559188 B1 20030506  
 AI US 2000-663264 20000915 (9)  
 PRAI US 2000-304196P 20000407 (60)  
 US 2000-240918P 20000309 (60)

US 1999-242911P 19990917 (60)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Weddington, Kevin E.  
LREP Thallemer, John D.  
CLMN Number of Claims: 11  
ECL Exemplary Claim: 1  
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)  
LN.CNT 2176

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide (I) ##STR1##

or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and diseases and conditions associated with diabetes; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition; the use of such combination or composition for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; the use of such combination or composition for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; and to a method of improving the bodily appearance of a warm-blooded animal.

L6 ANSWER 6 OF 32 USPATFULL on STN

AN 2003:106732 USPATFULL

TI Combinations comprising a beta-agonist and a further antidiabetic agent

IN Sanders Arch, Jonathan Robert, Welwyn Garden City, UNITED KINGDOM

PA SmithKline Beecham p.l.c. (non-U.S. corporation)

PI US 2003073644 A1 20030417

AI US 2002-243164 A1 20020913 (10)

RLI Continuation of Ser. No. US 2001-831651, filed on 11 Jul 2001, ABANDONED  
A 371 of International Ser. No. WO 1999-GB3755, filed on 11 Nov 1999,  
UNKNOWN

PRAI GB 1998-24789 19981111

GB 1998-24791 19981111

GB 1998-24790 19981111

DT Utility

FS APPLICATION

LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW 2220, P.O. Box  
1539, King of Prussia, PA, 19406-0939

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 769

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of a beta agonist and another antidiabetic agent, to a mammal in need thereof.

L6 ANSWER 7 OF 32 USPATFULL on STN

AN 2003:86880 USPATFULL

TI Drug comprising combination

IN Sugiyama, Yasuo, Kawanishi-shi, Hyogo, JAPAN

Odaka, Hiroyuki, Kobe-shi, Hyogo, JAPAN  
Naruo, Ken-ichi, Sanda-shi, Hyogo, JAPAN

PI US 2003060488 A1 20030327  
AI US 2002-203300 A1 20020809 (10)  
WO 2001-JP880 20010208  
PRAI JP 2000-38265 20000210  
DT Utility  
FS APPLICATION  
LREP WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800,  
WASHINGTON, DC, 20006-1021  
CLMN Number of Claims: 18  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1215  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A TNF-.alpha. inhibitor comprising an insulin sensitizer in combination  
with an HMG-CoA reductase inhibitor is useful as an agent for the  
prophylaxis or treatment of an inflammatory disease and the like.

L6 ANSWER 8 OF 32 USPATFULL on STN  
AN 2003:30867 USPATFULL  
TI Combined use of derivatives of GLP-1 analogs and PPAR ligands  
IN Knudsen, Liselotte Bjerre, Valby, DENMARK  
Wassermann, Karsten, Gentofte, DENMARK  
Sturis, Jeppe, Vaerlose, DENMARK  
Brand, Christian Lehn, Allerod, DENMARK

PI US 2003022816 A1 20030130  
AI US 2001-949344 A1 20010907 (9)  
RLI Continuation-in-part of Ser. No. US 2001-800541, filed on 7 Mar 2001,  
PENDING  
DT Utility  
FS APPLICATION  
LREP Reza Green, Esq., Novo Nordisk of North America, Inc., Suite 6400, 405  
Lexington Avenue, New York, NY, 10174-6401  
CLMN Number of Claims: 62  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 855  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods and compositions for treatment  
and/or prevention of type 1 and type 2 diabetes, dyslipdemia, impaired  
glucose tolerance, insulin resistance, obesity, and beta-cell apoptosis,  
as well as methods for increasing the size and number of beta-cells in a  
subject and/or stimulating beta-cell proliferation, which comprise  
administering both a stable GLP-1 analogue and a non-thiazolidinedione  
PPAR ligand.

L6 ANSWER 9 OF 32 USPATFULL on STN  
AN 2003:24218 USPATFULL  
TI Novel remedies with the use of beta 3 agonist  
IN Ogawa, Kohei, Shizuoka, JAPAN  
Umeno, Hiroshi, Shizuoka, JAPAN

PI US 2003018061 A1 20030123  
AI US 2002-182375 A1 20020729 (10)  
WO 2001-JP553 20010126  
PRAI JP 2000-20733 20000128  
DT Utility  
FS APPLICATION  
LREP YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202  
CLMN Number of Claims: 46  
ECL Exemplary Claim: 1  
DRWN No Drawings

LN.CNT 1675

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided is a therapeutic agent comprising at least one member selected from the group consisting of an anticholinergic agent, a monoamine reuptake inhibitor, a lipase inhibitor, a selective serotonin reuptake inhibitor, insulin, an insulin secretagogue, biguanide, an .alpha.-glucosidase inhibitor, an insulin resistance improving agent, a HMG-CoA reductase inhibitor, an anion exchange resin, a clofibrate type drug and a nicotinic acid type drug, and a compound having a .beta.3 agonist activity. The .beta.3-agonist has an activity of inhibiting dysuria. Further, when used together with a remedy for dysuria such as propiverine, oxybutynin hydrochloride or tolterodine, it exerts an enhanced anti-dysuria effect. When used together with an antiobestic agent such as sibutramine or orlistat, it exerts an enhanced antiobestic effect. When used together with an antidiabetic agent such as insulin, glibenclamide, acarbose or rosiglitazone, it exerts an enhanced antidiabetic effect. When used together with an antilipemic agent such as bezafibrate or pravastatin, it exerts an enhanced antilipemic effect.

L6 ANSWER 10 OF 32 USPATFULL on STN

AN 2002:330243 USPATFULL

TI Combined use of derivatives of GLP-1 analogs and PPAR ligands

IN Knudsen, Liselotte Bjerre, Valby, DENMARK

Wassermann, Karsten, Gentofte, DENMARK

Sturis, Jeppe, Vaerloose, DENMARK

Brand, Christian Lehn, Allerod, DENMARK

PI US 2002187926 A1 20021212

AI US 2001-951300 A1 20010913 (9)

RLI Continuation-in-part of Ser. No. US 2001-800541, filed on 7 Mar 2001, PENDING

DT Utility

FS APPLICATION

LREP Reza Green, Esq., Novo Nordisk of North America, Inc., Suite 6400, 405 Lexington Avenue, New York, NY, 10174-6401

CLMN Number of Claims: 74

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 896

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods and compositions for treatment and/or prevention of type 1 and type 2 diabetes, dyslipdemia, impaired glucose tolerance, insulin resistance, obeity, and beta-cell apoptosis, as well as methods for increasing the size and number of beta-cells in a subject and/or stimulating beta-cell proliferation, which comprise administering both a stable GLP-1 analogue and a non-thiazolidinedione PPAR ligand.

L6 ANSWER 11 OF 32 USPATFULL on STN

AN 2002:259463 USPATFULL

TI Methods and compositions for the treatment of alopecia and other disorders of the pilosebaceous apparatus

IN Krajcik, Rozlyn A., Poughquag, NY, UNITED STATES

Orentreich, Norman, New York, NY, UNITED STATES

PA Orentreich Foundation for the Advancement of Science, Inc., New York, NY, UNITED STATES (U.S. corporation)

PI US 2002143039 A1 20021003

AI US 2002-73607 A1 20020211 (10)

RLI Continuation of Ser. No. WO 2001-US5653, filed on 23 Feb 2001, UNKNOWN

PRAI US 2000-184398P 20000223 (60)

DT Utility

FS APPLICATION

LREP AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P., ONE COMMERCE SQUARE, 2005

MARKET STREET, SUITE 2200, PHILADELPHIA, PA, 19103

CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 772

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Insulin sensitivity increasing substances (ISIS), including but not limited to D-chiro-inositol, thiazolidinedione and derivatives, and biguanides, are useful in the treatment of hair loss and other disorders of the pilosebaceous apparatus (hirsutism, acne, etc.) associated with conditions of excess insulin and/or insulin resistance. The treatment comprises administering to a mammal, such as a human, at least one ISIS either alone or in combination with at least one agent, such as an androgen receptor blocker (ARB) and/or a steroid enzyme inhibitor or inducer (STI). Additionally, an activity enhancing agent may be included for topical administration.

L6 ANSWER 12 OF 32 USPATFULL on STN

AN 2002:251826 USPATFULL

TI Differentiating agents for the treatment of inflammatory intestinal diseases

IN Wu, Gary W., Ardmore, PA, UNITED STATES

PI US 2002137780 A1 20020926

AI US 2001-896984 A1 20010702 (9)

RLI Continuation-in-part of Ser. No. US 1999-457790, filed on 9 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1999-256165, filed on 23 Feb 1999, ABANDONED Continuation-in-part of Ser. No. US 1995-413806, filed on 30 Mar 1995, PATENTED Continuation-in-part of Ser. No. US 1995-387116, filed on 13 Feb 1995, PATENTED

DT Utility

FS APPLICATION

LREP LICATLA & TYRRELL P.C., 66 E. MAIN STREET, MARLTON, NJ, 08053

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN 2 Drawing Page(s)

LN.CNT 552

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for decreasing the inflammation associated with a chronic inflammatory intestinal condition in a patient is provided wherein the patient is administered an effective amount of a differentiating agent.

L6 ANSWER 13 OF 32 USPATFULL on STN

AN 2002:235080 USPATFULL

TI Peroxisome proliferator-activated receptor gamma ligand eluting medical device

IN Carlyle, Wenda, Petaluma, CA, UNITED STATES

Cheng, Peiwen, Santa Rosa, CA, UNITED STATES

Cafferata, Robert L., Santa Rosa, CA, UNITED STATES

PI US 2002127263 A1 20020912

AI US 2002-85539 A1 20020226 (10)

PRAI US 2001-271898P 20010227 (60)

DT Utility

FS APPLICATION

LREP Christine Aceves, Medtronic AVE, 3576 Unocal Place, Santa Rosa, CA, 95403

CLMN Number of Claims: 26

ECL Exemplary Claim: 1

DRWN 4 Drawing Page(s)

LN.CNT 947

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Implantable medical devices having an anti-restenotic coatings are disclosed. Specifically, implantable medical devices having coatings of

peroxisome proliferator-activated receptor gamma (PPAR.gamma.) agonists are disclosed. The anti-restenotic PPAR.gamma. ligands include thiazolidinedione compounds including ciglitazone. The anti-restenotic medial devices include stents, catheters, micro-particles, probes and vascular grafts. The medical devices can be coated using any method known in the art including compounding the thiazolidinedione with a biocompatible polymer prior to applying the coating. Moreover, medical devices composed entirely of biocompatible polymer-thiazolidinedione blends are disclosed. Additionally, medical devices having a coating comprising at least one thiazolidinedione in combination with at least one additional therapeutic agent are also disclosed. Furthermore, related methods of using and making the anti-restenotic implantable devices are also disclosed.

L6 ANSWER 14 OF 32 USPATFULL on STN  
AN 2002:209569 USPATFULL  
TI Use of RAR antagonists as modulators of hormone mediated processes  
IN Evans, Ronald M., La Jolla, CA, United States  
Tontoz, Peter J., Los Angeles, CA, United States  
Nagy, Laszlo, San Diego, CA, United States  
PA The Salk Institute for Biological Studies, La Jolla, CA, United States  
(U.S. corporation)  
PI US 6436993 B1 20020820  
US 2002137794 A1 20020926  
AI US 1999-352816 19990713 (9)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Jarvis, William; Assistant Examiner: Kim, Vickie  
LREP Reiter, Stephen E., Foley & Lardner  
CLMN Number of Claims: 14  
ECL Exemplary Claim: 1  
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)  
LN.CNT 936  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB In accordance with the present invention, it has been discovered that retinoic acid receptor (RAR) antagonists are capable of modulating processes mediated by other members of the steroid/thyroid hormone receptor superfamily, including permissive receptors such as PPARs (e.g., PPAR.alpha., PPAR.delta. and PPAR.gamma.). Indeed, it has been discovered that RAR antagonists, in combination with agonists for members of the steroid/thyroid hormone receptor superfamily, are capable of inducing and/or enhancing processes mediated by such members.

L6 ANSWER 15 OF 32 USPATFULL on STN  
AN 2002:198695 USPATFULL  
TI PAX8-PPARgamma nucleic acid molecules and polypeptides and uses thereof  
IN Fletcher, Jonathan A., Brookline, MA, UNITED STATES  
Kroll, Todd G., Newton Highlands, MA, UNITED STATES  
PI US 2002106796 A1 20020808  
AI US 2001-765111 A1 20010118 (9)  
PRAI US 2000-177109P 20000120 (60)  
US 2000-225079P 20000814 (60)  
DT Utility  
FS APPLICATION  
LREP Elizabeth R. Plumer, c/o Wolf, Greenfield & Sacks, P.C., Federal Reserve  
Plaza, 600 Atlantic Avenue, Boston, MA, 02210-2211  
CLMN Number of Claims: 62  
ECL Exemplary Claim: 1  
DRWN 6 Drawing Page(s)  
LN.CNT 3762  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB An oncogene designated PAX8-PPAR.gamma.1 contains a PAX8 coding region

fused to PPAR.gamma. coding region. Molecular characterization of PAX8-PPAR.gamma.1 molecules provides nucleotide and amino acid sequences useful for detection and treatment of certain tumors, particularly thyroid follicular carcinomas.

L6 ANSWER 16 OF 32 USPATFULL on STN  
AN 2002:99423 USPATFULL  
TI Treatment of diabetes with thiazolidinedione, insulin secretagogue and alpha glucosidase inhibitor  
IN Buckingham, Robin Edwin, Welwyn Garden City, UNITED KINGDOM  
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM  
PA SmithKline Beecham plc (non-U.S. corporation)  
PI US 2002052324 A1 20020502  
AI US 2001-989572 A1 20011120 (9)  
RLI Continuation of Ser. No. US 1999-445908, filed on 15 Dec 1999, PENDING A 371 of International Ser. No. WO 1998-GB2112, filed on 16 Jul 1998, UNKNOWN  
PRAI GB 1997-15298 19970718  
DT Utility  
FS APPLICATION  
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939  
CLMN Number of Claims: 22  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 487

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.

L6 ANSWER 17 OF 32 USPATFULL on STN  
AN 2002:88529 USPATFULL  
TI Metformin-containing compositions for the treatment of diabetes  
IN Fine, Stuart A., Northbrook, IL, United States  
Kinsella, Kevin J., La Jolla, CA, United States  
PA Akesis Pharmaceuticals, Inc., La Jolla, CA, United States (U.S. corporation)  
PI US 6376549 B1 20020423  
AI US 1998-156102 19980917 (9)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Criares, Theodore J.  
LREP Foley, Hoag & Eliot LLP  
CLMN Number of Claims: 40  
ECL Exemplary Claim: 1  
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)  
LN.CNT 1429

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods using same for the treatment of diabetes its sequelae and pre-diabetic conditions are provided. Invention compositions include the anti-diabetic agent metformin, and bioavailable sources of one or more of chromium, vanadium and magnesium. Also provided are pharmaceutical agents containing invention compositions and methods for administering such agents.

L6 ANSWER 18 OF 32 USPATFULL on STN  
AN 2002:67275 USPATFULL  
TI Combination therapeutic compositions and method of use

IN Jaen, Juan C., Burlingame, CA, UNITED STATES  
Chen, Jin-Long, Foster City, CA, UNITED STATES  
PI US 2002037928 A1 20020328  
AI US 2001-847887 A1 20010502 (9)  
PRAI US 2000-201613P 20000503 (60)  
DT Utility  
FS APPLICATION  
LREP TOWNSEND AND TOWNSEND AND CREW, TWO EMBARCADERO CENTER, EIGHTH FLOOR,  
SAN FRANCISCO, CA, 94111-3834  
CLMN Number of Claims: 51  
ECL Exemplary Claim: 1  
DRWN 7 Drawing Page(s)  
LN.CNT 1692

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides pharmaceutical compositions and methods for the treatment of diabetes mellitus using combination therapy. The compositions relate to a compound of Formula I and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, .alpha.-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of compound of Formula I with antidiabetic agent where the two components are delivered in a simultaneous manner, where the compound of Formula I is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound of Formula I.

L6 ANSWER 19 OF 32 USPATFULL on STN  
AN 2002:27439 USPATFULL  
TI Treatment of diabetes with thiazolidinedione, insulin secretagogue and diguanide  
IN Buckingham, Robin Edwin, Wel Wyn Garden City, UNITED KINGDOM  
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM  
PA SmithKline Beecham p.l.c. (non-U.S. corporation)  
PI US 2002016287 A1 20020207  
AI US 2001-939470 A1 20010824 (9)  
RLI Continuation of Ser. No. US 1999-446039, filed on 15 Dec 1999, PENDING A  
371 of International Ser. No. WO 1999-GB9802110, filed on 28 Jan 1999,  
UNKNOWN  
PRAI GB 1997-15295 19970718  
DT Utility  
FS APPLICATION  
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box  
1539, King of Prussia, PA, 19406-0939  
CLMN Number of Claims: 22  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 479

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an insulin secretagogue and a biguanide antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.

L6 ANSWER 20 OF 32 USPATFULL on STN  
AN 2002:22432 USPATFULL  
TI **Synergistic** effect of a sulfonylurea and/or non-sulfonylurea Kchannel blocker, and a phosphodiesterase 3 type inhibitor  
IN Fryburg, David A., East Lyme, CT, UNITED STATES  
Parker, Janice C., Ledyard, CT, UNITED STATES

PI US 2002013268 A1 20020131  
US 6610746 B2 20030826  
AI US 2001-829874 A1 20010410 (9)  
PRAI US 2000-196728P 20000413 (60)  
DT Utility  
FS APPLICATION  
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point  
Road, Groton, CT, 06340  
CLMN Number of Claims: 25  
ECL Exemplary Claim: 1  
DRWN 1 Drawing Page(s)  
LN.CNT 1475

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods of treating non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance, the methods comprising the step of administering to a patient having or at risk of having non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance a **synergistic** amount of: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also provides kits and pharmaceutical compositions that comprise: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also relates to kits and pharmaceutical compositions that comprise 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; 2) a cAMP phosphodiesterase type 3 inhibitor; and 3) an additional compound useful for the treatment of non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance.

L6 ANSWER 21 OF 32 USPATFULL on STN

AN 2002:12568 USPATFULL  
TI METHODS AND PHARMACEUTICAL COMPOSITIONS FOR INHIBITING TUMOR CELL GROWTH  
IN SPIEGELMAN, BRUCE M., WABAN, MA, UNITED STATES  
ALTIOK, SONER, BOSTON, MA, UNITED STATES  
MUELLER, ELISABETTA, BOSTON, MA, UNITED STATES  
SARRAF, PASHA, BOSTON, MA, UNITED STATES  
TONTONNOZ, PETER, SAN DIEGO, CA, UNITED STATES  
PA Dana-Farber Cancer Institute (U.S. corporation)  
PI US 2002006950 A1 20020117  
US 6552055 B2 20030422  
AI US 1997-923346 A1 19970904 (8)  
RLI Continuation of Ser. No. US 1996-766553, filed on 11 Dec 1996, ABANDONED  
DT Utility  
FS APPLICATION  
LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109  
CLMN Number of Claims: 48  
ECL Exemplary Claim: 1  
DRWN 16 Drawing Page(s)  
LN.CNT 2290

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is based on the finding that activation of PPAR.gamma. plays a key role in inducing growth arrest and

differentiation of certain actively proliferating cells. We show that administration of PPAR.gamma. agonists, such as thiazolidinedione ligands (TZDs), is effective both in vitro and in vivo at inhibiting the proiferation of such cells.

L6 ANSWER 22 OF 32 USPATFULL on STN  
AN 2002:12560 USPATFULL  
TI Methods of treating liver disorders and disorders associated with liver function  
IN Davis, Roger A., Solana Beach, CA, UNITED STATES  
PI US 2002006942 A1 20020117  
AI US 2001-792631 A1 20010223 (9)  
PRAI US 2000-184592P 20000224 (60)  
US 2000-187321P 20000306 (60)  
DT Utility  
FS APPLICATION  
LREP Robert M. Bedgood, PILLSBURY WINTHROP LLP, 50 Freemont Street, San Francisco, CA, 94105  
CLMN Number of Claims: 50  
ECL Exemplary Claim: 1  
DRWN 9 Drawing Page(s)  
LN.CNT 1499

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of treating liver inflammatory condition, disease or disorder are provided. Methods include administering amounts of a PPAR.gamma. agonist sufficient to ameliorate the inflammatory condition, disease or disorder. Methods of treating conditions associated with excess or undesirable cholesterol levels or decreased HDL levels or decreased CYP7A expression are also provided. Methods include administering amounts of a PPAR.gamma. agonist sufficient to decrease cholesterol levels or increase HDL levels or CYP7A expression.

L6 ANSWER 23 OF 32 USPATFULL on STN  
AN 2001:194440 USPATFULL  
TI Method of inhibiting angiogenesis  
IN Gerritsen, Mary E., San Mateo, CA, United States  
Xin, Xiaohua E., San Francisco, CA, United States  
PA Genentech, Inc. (U.S. corporation)  
PI US 2001036955 A1 20011101  
AI US 2001-865859 A1 20010525 (9)  
RLI Continuation of Ser. No. US 1999-443010, filed on 17 Nov 1999, ABANDONED  
PRAI US 1999-116530P 19990120 (60)  
US 1998-109328P 19981120 (60)  
DT Utility  
FS APPLICATION  
LREP BRINKS HOFER GILSON & LIONE, P.O. BOX 10395, CHICAGO, IL, 60610  
CLMN Number of Claims: 29  
ECL Exemplary Claim: 1  
DRWN 7 Drawing Page(s)  
LN.CNT 2090

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Angiogenesis is inhibited and the growth of tumors is treated by administering an effective amount of a PPAR gamma ligand/agonist, optionally with an RXR receptor ligand.

L6 ANSWER 24 OF 32 USPATFULL on STN  
AN 2001:158318 USPATFULL  
TI Method and composition for the treatment of diabetes  
IN Rieveley, Robert B., 4102 Yuculta Crescent, Vancouver, British Columbia, Canada V6N 3R5  
PI US 6291495 B1 20010918  
AI US 2000-608272 20000630 (9)

RLI Division of Ser. No. US 1997-804903, filed on 24 Feb 1997, now patented,  
Pat. No. US 6153632  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Weddington, Kevin E.  
LREP Oyen Wiggs Green & Mutala  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 503

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method of treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus.

L6 ANSWER 25 OF 32 USPATFULL on STN

AN 2001:82522 USPATFULL

TI Methods and pharmaceutical compositions for inhibiting tumor cell growth  
IN Spiegelman, Bruce M., Waban, MA, United States  
Altiok, Soner, Cambridge, MA, United States  
Mueller, Elisabetta, Boston, MA, United States  
Sarraf, Pasha, Boston, MA, United States  
Tontono, Peter, San Diego, CA, United States

PA Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)

PI US 6242196 B1 20010605

WO 9825598 19980618

AI US 1999-319769 19990917 (9)

WO 1997-US22879 19971211

19990917 PCT 371 date

19990917 PCT 102(e) date

DT Utility

FS Granted

EXNAM Primary Examiner: Leary, Louise N.

LREP Lahive & Cockfield, LLP, Mandragouras, Amy E., Smith, DeAnn F.

CLMN Number of Claims: 35

ECL Exemplary Claim: 1

DRWN 36 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 2761

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for inhibiting proliferation of a PPAR .gamma.-responsive hyperproliferative cell which comprises the step of contacting the cell with (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is disclosed. A method for treating or prophylactically preventing in an animal subject a disorder characterized by unwanted proliferation of PPAR.gamma.-responsive hyperproliferative cells which comprises administering to the subject (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is also disclosed. Pharmaceutical compositions comprising a therapeutically effective amount of a PPAR.gamma. agonist and a MAP kinase inhibitor are disclosed for use in the methods.

L6 ANSWER 26 OF 32 USPATFULL on STN

AN 2000:168044 USPATFULL

TI Treatment of arteriosclerosis and xanthoma

IN Tsujita, Yoshio, Tokyo, Japan

Horikoshi, Hiroyoshi, Tokyo, Japan

Shiomi, Masashi, Kobe, Japan  
Ito, Takashi, Kobe, Japan  
PA Sankyo Company, Limited, Tokyo, Japan (non-U.S. corporation)  
PI US 6159997 20001212  
AI US 1998-61446 19980416 (9)  
RLI Division of Ser. No. US 1996-676090, filed on 2 Jul 1996, now patented,  
Pat. No. US 5798375  
PRAI JP 1995-167291 19950703  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Criares, Theodore J.  
LREP Frishauf, Holtz, Goodman, Langer & Chick, P.C.  
CLMN Number of Claims: 210  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1910

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A combination of one or more HMG-CoA reductase inhibitors (for example pravastatin, lovastatin, simvastatin, fluvastatin, rivastatin or atorvastatin) with one or more insulin sensitizers (for example troglitazone, pioglitazone, englitazone, BRL-49653, 5-(4-(2-[1-(4-2'-pyridylphenyl)ethylideneaminoxy]ethoxy)benzyl)thiazolidine-2,4-dione, 5-(4-(5-methoxy-3-methylimidazo[5,4-b]pyridin-2-ylmethoxy)benzyl)thiazolidine-2,4-dione or its hydrochloride, 5-[4-(6-methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, 5-[4-(1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and 5-[4-(5-hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione) exhibits a **synergistic** effect and is significantly better at preventing and/or treating arteriosclerosis and/or xanthoma than is either of the components of the combination alone.

L6 ANSWER 27 OF 32 USPATFULL on STN

AN 2000:161029 USPATFULL

TI Method and composition for the treatment of diabetes

IN Rieveley, Robert B., 4102 Yuculta Crescent, Vancouver, British Columbia, Canada V6N 3R5

PI US 6153632 20001128

AI US 1997-804903 19970224 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Oyen Wiggs Green & Mutala

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 497

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method of treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus.

L6 ANSWER 28 OF 32 USPATFULL on STN

AN 2000:67567 USPATFULL

TI Modulators of ob gene and screening methods therefor

IN Briggs, Michael R., Downingtown, PA, United States

Auwerx, Johan, Millionfosse, France

de Vos, Piet, Zingem, Belgium  
Staels, Bart, Kraainem, Belgium  
Croston, Glenn E., San Diego, CA, United States  
Miller, Stephen G., San Diego, CA, United States

PA Ligand Pharmaceuticals Incorporated, San Diego, CA, United States (U.S. corporation)

PI US 6068976 20000530

AI US 1996-618100 19960319 (8)

RLI Continuation-in-part of Ser. No. US 1995-558588, filed on 30 Oct 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-510584, filed on 2 Aug 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-418096, filed on 5 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-408584, filed on 20 Mar 1995, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Yucel, Remy

LREP Lyon & Lyon LLP

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN 48 Drawing Figure(s); 21 Drawing Page(s)

LN.CNT 3662

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the isolation and cloning of the promoter and other control regions of a human ob gene. It provides a method for identifying and screening for agents useful for the treatment of diseases and pathological conditions affected by the level of expression of an ob gene. These agents interact directly or indirectly with the promoter or other control regions of the ob gene. A PPAR.gamma. agonist, BRL49653, has been identified to be useful in treating anorexia, cachexia, and other diseases characterized by insufficient food intake or body weight loss. Modulators of ob gene expression may be used to treat other diseases such as obesity, diabetes, hypertension, cardiovascular diseases and infertility.

L6 ANSWER 29 OF 32 USPATFULL on STN

AN 2000:1892 USPATFULL

TI Combinations for diabetes

IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States

PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

PI US 6011049 20000104

AI US 1998-189132 19981109 (9)

RLI Continuation-in-part of Ser. No. US 1997-970057, filed on 13 Nov 1997, now patented, Pat. No. US 5859037

PRAI US 1997-38224P 19970219 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Jordan, Kimberly

LREP Ashbrook, Charles W.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 12 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 974

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combinations of a glitazone antidiabetic agent and a biguanide antidiabetic agent, and optionally a sulfonylurea antidiabetic agent, are useful for treating diabetes mellitus and improving glycemic control.

L6 ANSWER 30 OF 32 USPATFULL on STN

AN 1999:132855 USPATFULL

TI Sulfonylurea-glitazone combinations for diabetes  
IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States  
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S.  
corporation)  
PI US 5972973 19991026  
AI US 1998-173911 19981016 (9)  
RLI Continuation-in-part of Ser. No. US 1997-970057, filed on 13 Nov 1997,  
now patented, Pat. No. US 5859037  
PRAI US 1997-38224P 19970219 (60)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Jordan, Kimberly  
LREP Ashbrook, Charles W.  
CLMN Number of Claims: 6  
ECL Exemplary Claim: 1  
DRWN 7 Drawing Figure(s); 7 Drawing Page(s)  
LN.CNT 733  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Combinations of a sulfonylurea antidiabetic agent and a glitazone  
antidiabetic agent are useful for treating diabetes mellitus and  
improving glycemic control.

L6 ANSWER 31 OF 32 USPATFULL on STN  
AN 1999:4694 USPATFULL  
TI Sulfonylurea-glitazone combinations for diabetes  
IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States  
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S.  
corporation)  
PI US 5859037 19990112  
AI US 1997-970057 19971113 (8)  
PRAI US 1997-38224P 19970219 (60)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Jordan, Kimberly  
LREP Ashbrook, Charles W.  
CLMN Number of Claims: 8  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Figure(s); 6 Drawing Page(s)  
LN.CNT 1902  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Combinations of a sulfonylurea antidiabetic agent and a glitazone  
antidiabetic agent are useful for treating diabetes mellitus and  
improving glycemic control.

L6 ANSWER 32 OF 32 USPATFULL on STN  
AN 1998:101666 USPATFULL  
TI Treatment of arteriosclerosis and xanthoma  
IN Tsujita, Yoshio, Tokyo, Japan  
Horikoshi, Hiroyoshi, Kobe, Japan  
Ito, Takashi, Kobe, Japan  
PA Sankyo Company, Limited, Tokyo, Japan (non-U.S. corporation)  
PI US 5798375 19980825  
AI US 1996-676090 19960702 (8)  
PRAI JP 1995-167291 19950703  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Criares, Theodore J.  
LREP Frishauf, Holtz, Goodman, Langer & Chick, Esq.  
CLMN Number of Claims: 6  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1158

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A combination of one or more HMG-CoA reductase inhibitors (for example pravastatin, lovastatin, simvastatin, fluvastatin, rivastatin or atorvastatin) with one or more insulin sensitizers (for example troglitazone, pioglitazone, englitazone, BRL-49653, 5-(4-{2-[1-(4-2'-pyridylphenyl)ethylideneaminoxy]-ethoxy}benzyl)thiazolidine-2,4-dione, 5-(4-(5-methoxy-3-methylimidazo[5,4-b]pyridin-2-yl-methoxy)benzyl)thiazolidine-2,4-dione or its hydrochloride, 5-[4-(6-methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, 5-[4-(1-methylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione and 5-[4-(5-hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione) exhibits a **synergistic** effect and is significantly better at preventing and/or treating arteriosclerosis and/or xanthoma than is either of the components of the combination alone.

=> s 12 and glimepiride

357 GLIMEPIRIDE

L7 34 L2 AND GLIMEPIRIDE

=> s 12 and metformin

1050 METFORMIN

L8 54 L2 AND METFORMIN

=> s 17 and 18

L9 27 L7 AND L8

=> d 19 1-27 bib, ab, kwic

L9 ANSWER 1 OF 27 USPATFULL on STN

AN 2003:201447 USPATFULL

TI Combinations comprising dipeptidylpeptidase-iv inhibitor

IN Balkan, Bork, Madison, CT, UNITED STATES

Hughes, Thomas Edward, Somerville, NJ, UNITED STATES

Holmes, David Grenville, Binningen, SWITZERLAND

Villhauer, Edwin Bernard, Morristown, NJ, UNITED STATES

PI US 2003139434 A1 20030724

AI US 2002-181169 A1 20021010 (10)

WO 2001-EP590 20010119

PRAI US 2000-9489234 20000121

US 2000-9619262 20000719

DT Utility

FS APPLICATION

LREP THOMAS HOXIE, NOVARTIS, PATENT AND TRADEMARK DEPARTMENT, ONE HEALTH

PLAZA 430/2, EAST HANOVER, NJ, 07936-1080

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1581

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors,

insulin sensitivity enhancers, insulin secretion enhancers, .alpha.-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and .alpha..sub.2-adrenergic antagonists, for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

SUMM . . . agonists of UCPs, antidiabetic thiazolidinediones (glitazones), non-glitazone type PPAR.gamma. agonists, dual PPAR.gamma./PPAR.alpha. agonists, antidiabetic vanadium containing compounds and biguanides, e.g., **metformin**.

SUMM [0089] The insulin sensitivity enhancer is preferably selected from the group consisting of antidiabetic thiazolidinediones, antidiabetic vanadium containing compounds and **metformin**.

SUMM [0090] In one preferred embodiment, the insulin sensitivity enhancer is **metformin**.

SUMM [0122] The preparation of **metformin** (dimethyldiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. **Metformin**, can be administered e.g. in the form as marketed under the trademarks GLUCOPHAGE.TM..

SUMM . . . is, for example, glisoxepid, glyburide, glibenclamide, acetoexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably **glimepiride** or gliclazide.

Tolbutamide, glibenclamide, gliclazide, glibornuride, gliquidone, glisoxepid and **glimepiride** can be administered e.g. in the form as they are marketed under the trademarks RASTINON HOECHST.TM., AZUGLUCON.TM., DIAMICRONT.TM., GLUBORID.TM., GLURENORM.TM., . . .

SUMM . . . is selected from (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine and (S)-1-[2-[5-cyanopyridin-2-yl)amino]ethyl-aminoacetyl)-2-cyano-pyrrolidine, and the further antidiabetic compound is selected from the group consisting of nateglinide, repaglinide, **metformin**, rosiglitazone, pioglitazone, troglitazone, glisoxepid, glyburide, glibenclamide, acetoexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, **glimepiride** and gliclazide, or the pharmaceutically acceptable salt of such a compound.

SUMM . . . derivative nateglinide is chosen for the study, matching placebos are preferably administered before breakfast, lunch and dinner period 1. If **metformin** is chosen for the study, matching placebos are preferably administered before breakfast and dinner.

SUMM . . . thiazolidinedione troglitazone, the antidiabetic phenylacetic acid derivative repaglinide, the .alpha.-glucosidase inhibitor acarbose, the antidiabetic D-phenylalanine derivative nateglinide or the biguanide **metformin** is chosen as the combination partner.

SUMM [0175]

TABLE 5

DPP728 plus **metformin**

**metformin** 500 mg\*\* + DPP728 placebo\*  
DPP728 50 mg\* + **metformin** placebo\*\*  
**metformin** 500 mg\*\* + DPP728 50 mg\*  
**metformin** placebo\*\* + DPP728 placebo\*

\*administered before breakfast, lunch, and dinner

\*\*administered before breakfast and dinner

SUMM . . . contain either 120 mg or matching placebo. Troglitazone 200 mg tablets, repaglinide 1 mg tablets, acarbose 50 mg tablets and **metformin** 500 mg tablets can be purchased commercially and overencapsulated to match the corresponding placebo capsules.

SUMM . . . 20:1 and 1:24,  
preferably between 2:1 and 1:2,  
e.g. 1:1  
Troglitazone between 1:1 and 1:10,  
preferably between 1:2 and 1:6,  
e.g. 1:4  
**Metformin** between 4:1 and 1:60,  
preferably between 1:1 and 1:10,  
e.g. 1:6  
Repaglinide between 100:1 and 15:1,  
preferably between 60:1 and 20:1,

. . .  
SUMM . . . mg/day  
glibornuride about 5 to 150 mg/day about 12.5 to 75  
mg/day  
gliclazide about 20 to 480 mg/day about 80 to 240  
mg/day  
**glimepiride** about 0.25 to 12 mg/day about 1  
to 6 mg/day  
gliquidone about 5 to 250 mg/day about 30 to 120  
mg/day  
glisoxepid. . . day  
KRP297 about 0.1 to 2500 mg/day about 1 to 1000  
mg/day  
MCC555 about 0.1 to 2000 mg/day about 0.5 to 100  
mg/day  
**metformin** about 250 to 1500 mg/day about 500  
to 1250, e.g.  
1000, mg/day  
miglitol about 50 to 500 mg/day about 100 to. . .

CLM What is claimed is:

. . . is selected from (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine and (S)-1-(2-[5-cyanopyridin-2-yl]amino)ethyl-aminoacetyl)-2-cyano-pyrrolidine, and the further antidiabetic compound is selected from the group consisting of nateglinide, repaglinide, **metformin**, rosiglitazone, pioglitazone, troglitazone, glisoxepid, glyburide, glibenclamide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, **glimepiride** and gliclazide, or the pharmaceutically acceptable salt of such a compound.

IT 64-77-7, Tolbutamide 94-20-2, Chloropropamide 339-43-5, Carbutamide 451-71-8, Glyhexamide 657-24-9, Metformin 664-95-9, Tolcyclamide 673-06-3D, D-Phenylalanine, derivs. 968-81-0, Acetohexamide 1156-19-0, Tolazamide 3149-00-6, Phenbutamide 7440-62-2D, Vanadium, compds., biological studies 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 25046-79-1, Glisoxepid 26944-48-9, Glibornuride 29094-61-9, Glipizide 33342-05-1, Gliquidone 93479-97-1, Glimepiride 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 135062-02-1, Repaglinide 247016-69-9 274901-16-5  
(combinations comprising dipeptidylpeptidase-IV inhibitor)

AN 2003:166531 USPATFULL  
 TI Combination of organic compounds  
 IN Webb, Randy Lee, Flemington, NJ, UNITED STATES  
 PI US 2003114389 A1 20030619  
 AI US 2002-290651 A1 20021108 (10)  
 PRAI US 2001-350708P 20011113 (60)  
 DT Utility  
 FS APPLICATION  
 LREP THOMAS HOXIE, NOVARTIS, CORPORATE INTELLECTUAL PROPERTY, ONE HEALTH  
 PLAZA 430/2, EAST HANOVER, NJ, 07936-1080  
 CLMN Number of Claims: 7  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 601  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to a combination, such as a combined preparation  
 or pharmaceutical composition, respectively, comprising the renin  
 inhibitor of formula (I) or a pharmaceutically acceptable salt thereof  
 and at least one antidiabetic agent.  
 SUMM . . . [(S)-2-ethoxy-4-(2-[[3-methyl-1-[2-(1-  
 piperidinyl)phenyl]butyl]amino]-2-oxoethyl)benzoic acid--cf. EP 589874];  
 calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylicarbonyl)-  
 propionate dihydrate (mitiglinide--cf. EP 507534); furthermore  
 representatives of the new generation of SUs such as **glimepiride**  
 (cf. EP 31058); and in free or pharmaceutically acceptable salt form.  
 SUMM [0018] A preferred insulin sensitizer is **metformin** or a  
 pharmaceutically acceptable salt thereof such as the mono-hydrochloride.  
 SUMM . . . pharmaceutically accepted salt thereof and as second active  
 agent an active agent selected from the group consisting of nateglinide,  
 repaglinide, **metformin**, the compounds that is specifically  
 disclosed in Example 3 of WO 98/19998 or in Example 1 of WO 00/34241,  
 respectively,. . .  
 SUMM [0075] The insulin sensitizer **metformin** is preferably  
 administered in a dosage range of about 100 mg to about 1200 mg per dose  
 unit, especially 500 mg, 850 mg or 1000 mg. In a low dose combination,  
**metformin** is preferably administered in a dosage of 125 mg, 250  
 mg or 500 mg.  
 CLM What is claimed is:  
 5. A composition according to claim 2 wherein an insulin sensitizer is  
 selected from the group consisting of **metformin** or a  
 pharmaceutically acceptable salt thereof and an appropriate hypoglycemic  
 thiazolidinedione derivative.  
 . . . or a pharmaceutically acceptable salt thereof and at least one  
 antidiabetic agent selected from the group consisting of nateglinide,  
 repaglinide, **metformin**, the compound that is specifically  
 disclosed in Example 3 of WO 98/19998, the compound that is specifically  
 disclosed in Example. . .  
 IT 657-24-9, Metformin 105816-04-4, Nateglinide 111025-46-8,  
 Pioglitazone **122320-73-4**, Rosiglitazone 135062-02-1,  
 Repaglinide 145375-43-5, Mitiglinide 173334-57-1, Aliskiren  
 173334-58-2  
 (pharmaceutical compns. contg. renin inhibitor and antidiabetics)  
 L9 ANSWER 3 OF 27 USPATFULL on STN  
 AN 2003:134647 USPATFULL  
 TI Substituted azole acid derivatives useful as antidiabetic and  
 antiobesity agents and method  
 IN Cheng, Peter T., Princeton, NJ, UNITED STATES  
 Zhang, Hao, Belle Mead, NJ, UNITED STATES  
 Hariharan, Narayanan, Richboro, PA, UNITED STATES  
 PI US 2003092736 A1 20030515

AI US 2002-153454 A1 20020522 (10)  
PRAI US 2001-294380P 20010530 (60)  
DT Utility  
FS APPLICATION  
LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O  
BOX 4000, PRINCETON, NJ, 08543-4000  
CLMN Number of Claims: 20  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Page(s)  
LN.CNT 3412  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Compounds are provided which have the structure ##STR1##

wherein Q is C or N; R.sup.2a, R.sup.2b, R.sup.2c, X.sub.1 to X.sub.7, R.sup.1, R.sup.2, R.sup.3, R.sup.3a, R.sup.4, A, Y, m, and n are as defined herein, which compounds are useful as antidiabetic, hypolipidemic, and antiobesity agents. The present invention further provides a method for treating obesity and dyslipidemia in mammals including humans through simultaneous inhibition of peroxisome proliferator activated receptor-.gamma. (PPAR.gamma.) and stimulation of peroxisome proliferator activated receptor-.alpha. (PPAR.alpha.).

SUMM . . . or combination of compounds that antagonize PPAR.gamma., activates PPAR.alpha. activity, an anti-diabetic compound such as but not limited to insulin, **metformin**, insulin sensitizers, sulfonylureas, aP2 inhibitor, SGLT-2 inhibitor, a lipid-lowering agent such as but not limited to statins, fibrates, niacin ACAT. . .

DETD . . . the use of a combination of a dual PPAR.gamma. antagonist/PPAR.alpha. agonist with anti-diabetic agents such as but not limited to **metformin**, sulfonylurea, insulin, insulin sensitizers, aP2 inhibitor, SGLT2 inhibitor, agents that affect liver glucose output, a lipid lowering agent such as. . .

DETD [0174] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

DETD [0176] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

DETD [0184] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

DETD [0185] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

DETD . . . tested in the disease models described above, in combination with an anti diabetic agent such as but not limited to **metformin** and sulfonylurea and/or a lipid lowering agent such as PPAR.alpha. agonists (such as, but not limited to fenofibrate and gemfibrozil). . .

CLM What is claimed is:

15. The combination as defined in claim 12 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide,. . .

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-53-9, Verapamil 58-32-2, Dipyrindamole 59-67-6, Niacin, biological studies 94-20-2, Chlorpropamide 122-09-8, Phentermine 525-66-6, Propranolol 637-07-0, Clofibrate 657-24-9, Metformin 4205-91-8, Clonidine

hydrochloride 9004-10-8, Insulin, biological studies 10238-21-8,  
 Glyburide 14838-15-4, Phenylpropanolamine 19237-84-4, Prazosin  
 hydrochloride 21187-98-4, Glliclazide 21829-25-4, Nifedipine  
 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide  
 42200-33-9, Nadolol 49562-28-9, Fenofibrate 55142-85-3, Ticlopidine  
 56180-94-0, Acarbose 62571-86-2, Captopril 72432-03-2, Miglitol  
 72956-09-3, Carvedilol 75330-75-5, Lovastatin 75847-73-3, Enalapril  
 76547-98-3, Lisinopril 79902-63-9, Simvastatin 80830-42-8, Fentiapril  
 81093-37-0, Pravastatin 85441-61-8, Quinapril 86541-75-5, Benazepril  
 87333-19-5, Ramipril 93479-97-1, Glimepiride 93957-54-1, Fluvastatin  
 96829-58-2, Orlistat 97240-79-4, Topiramate 98048-97-6, Fosinopril  
 103775-10-6, Moexipril 105816-04-4, Nateglinide 106650-56-0,  
 Sibutramine 111025-46-8, Pioglitazone 111470-99-6, Amlodipine  
 besylate 113665-84-2, Clopidogrel 114798-26-4, Losartan  
**122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin  
 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6,  
 Irbesartan 143443-90-7, Ifetroban 144288-97-1, Ts-962 145599-86-6,  
 Cerivastatin 152755-31-2, Ly295427 159183-92-3, 1750355  
 160135-92-2, Gemopatrilat 166518-60-1, Avasimibe 167305-00-2,  
 Omapatrilat 169319-62-4, Cgs 30440 170861-63-9, Jtt-501  
 178759-95-0, MD 700 182815-44-7, Cholestagel 196808-45-4  
 199113-98-9, Nn-2344 199914-96-0, Ym-440 213252-19-8, Krp297  
 244081-42-3, Aj9677 251572-86-8, p32/98 287714-41-4 335149-08-1,  
 1895645 335149-14-9, r-119702 335149-15-0, Kad1129 335149-17-2,  
 Arho39242 335149-19-4, Gw-409544 335149-23-0, Nvp-dpp-728a  
 335149-24-1, Atl-962 335149-25-2, Cp331648 416839-88-8, Axokine  
 430433-17-3, Glipyrade 430433-39-9, Isaglitazone  
 (coadministration; prepn. of azolecarboxylic acids useful as  
 antidiabetic and antiobesity agents)

L9 ANSWER 4 OF 27 USPATFULL on STM  
 AN 2003:134608 USPATFULL  
 TI Conformationally constrained analogs useful as antidiabetic and  
 antiobesity agents and method  
 IN Cheng, Peter T., Princeton, NJ, UNITED STATES  
 Jeon, Yoon, Belle Mead, NJ, UNITED STATES  
 Wang, Wei, Princeton, NJ, UNITED STATES  
 PI US 2003092697 A1 20030515  
 AI US 2002-153342 A1 20020522 (10)  
 PRAI US 2001-294505P 20010530 (60)  
 DT Utility  
 FS APPLICATION  
 LREP Stephen B. Davis, Bristol-Myers Squibb Company, Patent Department, P.O.  
 Box 4000, Princeton, NJ, 08543-4000  
 CLMN Number of Claims: 34  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 2127  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB Compounds are provided which have the structure ##STR1##

wherein Q is C or N, X.sub.1 is C or N, and R.sup.1, R.sup.2, R.sup.2a,  
 R.sup.2b, R.sup.2c, R.sup.3, Y, A, m, n, X.sub.2, X.sub.3 and X.sub.4  
 are as defined herein, which compounds are useful as antidiabetic,  
 hypolipidemic, and antiobesity agents.

SUMM [0126] The other antidiabetic agent may be an oral antihyperglycemic  
 agent preferably a biguanide such as **metformin** or phenformin  
 or salts thereof, preferably **metformin** HCl.

SUMM [0128] The other antidiabetic agent may also preferably be a sulfonyl  
 urea such as glyburide (also known as glibenclamide),  
**glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide,  
 glliclazide or chlorpropamide, other known sulfonylureas or other

antihyperglycemic agents which act on. . .

SUMM [0136] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipyrizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0137] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:

20. The combination as defined in claim 19 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipyrizide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide,. . .

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-53-9, Verapamil 58-32-2, Dipyrizidamole 59-67-6, Niacin, biological studies 94-20-2, Chlorpropamide 122-09-8, Phentermine 525-66-6, Propranolol 637-07-0, Clofibrate 657-24-9, Metformin 4205-91-8, Clonidine hydrochloride 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 19237-84-4, Prazosin hydrochloride 21187-98-4, Gliclazide 21829-25-4, Nifedipine 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 42200-33-9, Nadolol 49562-28-9, Fenofibrate 54870-28-9, Meglitinide 55142-85-3, Ticlopidine 56180-94-0, Acarbose 62571-86-2, Captopril 72432-03-2, Miglitol 72956-09-3, Carvedilol 75330-75-5, Lovastatin 75847-73-3, Enalapril 76547-98-3, Lisinopril 79902-63-9, Simvastatin 80830-42-8, Fentiapril 81093-37-0, Pravastatin 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 98048-97-6, Fosinopril 103775-10-6, Moexipril 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 111470-99-6, Amlodipine besylate 113665-84-2, Clopidogrel 114798-26-4, Losartan **122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 141758-74-9, AC 2993 143443-90-7, Ifetroban 144288-97-1, TS-962 145599-86-6, Cerivastatin 147511-69-1 152755-31-2, LY295427 159183-92-3, L750355 160135-92-2, Gemopatrilat 166518-60-1, Avasimibe 167305-00-2, Omapatrilat 169319-62-4, CGS 30440 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 182815-44-7, Cholestagel 196808-45-4, GI 262570 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 251565-85-2, AR-H 039242 251572-86-8, P32/98 287714-41-4 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-19-4, GW-409544 335149-23-0, NVP-DPP-728A 335149-24-1, ATL-962 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipyrizide 430433-39-9, Isaglitazone (coadministration; prepn. of oxazolylethoxyphenylprolines and related compds. as antidiabetic and antiobesity agents)

L9 ANSWER 5 OF 27 USPATFULL on STN

AN 2003:127628 USPATFULL

TI O-pyrazole glucoside SGLT2 inhibitors and method of use

IN Washburn, William N., Titusville, NJ, UNITED STATES

PI US 2003087843 A1 20030508

AI US 2002-235336 A1 20020905 (10)

PRAI US 2001-317280P 20010905 (60)

DT Utility

FS APPLICATION

LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000

CLMN Number of Claims: 18

ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1236  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB A compound of formula I ##STR1##

wherein

A is CH.sub.2 or (CH.sub.2).sub.2;

R.sup.1 is hydrogen, arylalkyl, alkenyl, or alkyl;

R2 is alkyl or perfluoroalkyl; and

R.sup.3 and R.sup.4 are as defined herein.

Further provided are methods of using such compounds for the treatment of diabetes and related diseases, and to pharmaceutical compositions containing such compounds.

SUMM . . . novel, safe, and orally active antidiabetic agents is also desired in order to complement existing therapies, including the sulfonylureas, thiazolidinediones, **metformin**, and insulin, and to avoid the potential side effects associated with the use of these other agents.

SUMM [0121] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., **metformin** or phenformin), glucosidase inhibitors (e.g., acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., **glimepiride**, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance.RTM.), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR. . .

SUMM [0158] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:

. . . as defined in claim 8 wherein the antidiabetic agent is at least one agent selected from the group consisting of **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, . . .

IT 94-20-2, Chlorpropamide 637-07-0, Clofibrate 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 21187-98-4, Gliclazide 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 141750-63-2, Nisvastatin 141758-74-9, AC 2993 144288-97-1, TS-962 145599-86-6, Cerivastatin 152755-31-2, LY295427 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 251565-85-2, AR-H 039242 262352-17-0, CP 529414 287714-41-4, Visastatin 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-19-4, GW-409544 335149-23-0, NVP-DPP-728A 430433-17-3, Glipiride 430433-39-9, Isaglitazone (prepn. of O-pyrazole glucoside SGLT2 inhibitors as antidiabetic agents)

L9 ANSWER 6 OF 27 USPATFULL on STN  
 AN 2003:123367 USPATFULL  
 TI Method of treating metabolic disorders especially diabetes, or a disease  
 or condition associated with diabetes  
 IN Gatlin, Marjorie Regan, Hoboken, NJ, United States  
 Ball, Michele Ann, Morris Plains, NJ, United States  
 Mannion, Richard Owen, Mount Arlington, NJ, United States  
 Karnachi, Anees Abdulquadar, Hillsborough, NJ, United States  
 Guitard, Christiane, Hegenheim, FRANCE  
 Allison, Malcolm, Basel, SWITZERLAND  
 PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)  
 PI US 6559188 B1 20030506  
 AI US 2000-663264 20000915 (9)  
 PRAI US 2000-304196P 20000407 (60)  
 US 2000-240918P 20000309 (60)  
 US 1999-242911P 19990917 (60)  
 DT Utility  
 FS GRANTED  
 EXNAM Primary Examiner: Weddington, Kevin E.  
 LREP Thallemer, John D.  
 CLMN Number of Claims: 11  
 ECL Exemplary Claim: 1  
 DRWN 0 Drawing Figure(s); 0 Drawing Page(s)  
 LN.CNT 2176  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to a combination, such as a combined preparation  
 or pharmaceutical composition, respectively, which comprises nateglinide  
 (I) ##STR1##

or repaglinide and at least one other antidiabetic compound selected  
 from the group consisting of thiazolidinedione derivatives (glitazones),  
 sulfonyl urea derivatives and **metformin** for simultaneous,  
 separate or sequential use in the prevention, delay of progression or  
 treatment of diseases, especially metabolic disorders and in particular  
 type 2 diabetes and diseases and conditions associated with diabetes; to  
 a composition, respectively, which comprises nateglinide and a  
 pharmaceutically acceptable carrier and to a process of making such  
 composition; the use of such combination or composition for the  
 preparation of a medicament for the prevention, delay of progression or  
 treatment of metabolic disorders; a method of prevention, delay of  
 progression or treatment of diseases in warm-blooded animals; the use of  
 such combination or composition for the cosmetic treatment of a mammal  
 in order to effect a cosmetically beneficial loss of body weight; and to  
 a method of improving the bodily appearance of a warm-blooded animal.

AB . . . and at least one other antidiabetic compound selected from the  
 group consisting of thiazolidinedione derivatives (glitazones), sulfonyl  
 urea derivatives and **metformin** for simultaneous, separate or  
 sequential use in the prevention, delay of progression or treatment of  
 diseases, especially metabolic disorders and. . .  
 SUMM . . . and at least one other antidiabetic compound selected from the  
 group consisting of thiazolidinedione derivatives (glitazones), sulfonyl  
 urea derivatives and **metformin** for simultaneous, separate or  
 sequential use in the prevention, delay of progression or treatment of  
 diseases, especially metabolic disorders and. . .  
 SUMM . . . and at least one other antidiabetic compound selected from the  
 group consisting of thiazolidinedione derivatives (glitazones), sulfonyl  
 urea derivatives and **metformin**, in which the active  
 ingredients are present in each case in free form or in the form of a  
 pharmaceutically. . .  
 SUMM . . . or repaglinide and at least one other antidiabetic compound  
 selected from the group consisting of glitazones, sulfonyl urea

derivatives and **metformin**, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically. . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or. . . nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl ureas and **metformin**, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect. . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin**, and especially a strong synergism between nateglinide or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin**.

SUMM . . . derivative is, for example, glisoxepid, glyburide, acetohehexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably **glimepiride** or gliclazide.

SUMM . . . ACTOS.TM.. Ciglitazone can, for example, be formulated as disclosed in Example 13 of U.S. Pat. No. 4,287,200. If the drug **metformin** shall be administered in a separate pharmaceutical composition, it can be administered in the form as it is launched e.g. under the trademark DIABETOSAN.TM.. If the drug **metformin** shall be administered in a separate pharmaceutical composition in the form of its hydrochloride salt, the **metformin** hydrochloride salt can be administered in the form as it is launched e.g. under the trademarks DIABETASE 500.TM., DIABETASE 850.TM.. . . the trademark AZUGLUCON.TM. or EUGLUCON.TM.. Tolbutamide can be administered in the form as it is launched under the trademark ORABET, **glimepiride** as launched under the trademark AMARYL.TM., gliclazide as launched under the trademark DIAMICRON.TM., glibornuride as launched under the trademark GLUBORID.TM.. . .

SUMM . . . other antidiabetic compound selected from the group consisting of glitazones, in particular rosiglitazone, troglitazone and pioglitazone, sulfonyl urea derivatives and **metformin** results not only in a beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the combined. . .

SUMM . . . compound selected from the group consisting of glitazones, in particular rosiglitazone, rosiglitazone and pioglitazone, sulfonyl urea derivatives and the biguanide **metformin**, or in each case a pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of diseases,. . .

SUMM . . . are, in particular, suitable to assess the effects of monotherapy with nateglinide, repaglinide, a glitazone, a sulfonyl urea derivative or **metformin** and a combination of nateglinide or repaglinide with one or more compounds selected from the group consisting of a glitazones, a sulfonyl urea derivatives or **metformin** on glycemic control. The studies are especially suitable to assess the effects of monotherapy with **metformin** or the corresponding hydrochloride salt or a combination of nateglinide and **metformin** or the corresponding hydrochloride salt on glycemic control. Subjects with a diagnosis of type 2 diabetes who have not achieved. . . are chosen for this trial. The effects on glycemic control achieved with nateglinide monotherapy, monotherapy with a glitazone, monotherapy with **metformin** and the combination therapies as given below are determined in these studies after 16 or 24 weeks with the control. . .

SUMM Study 3: Combination of 60 mg Nateglinide and 250 mg of **Metformin** Administered as a Single Pharmaceutical Composition

SUMM

Treatment Group Treatment

- 1 60 mg nateglinide
- 2 250 mg **metformin**
- 3 60 mg nateglinide + 250 mg **metformin**
- 4 placebo only

SUMM Study 4: Combination of 60 or 120 mg Nateglinide Before Meals and 1000 mg of **Metformin** as a Daily Dosis

SUMM Subjects with HbA<sub>1c</sub> values of 6.8-11% receive **metformin** for at least 3 months und at least 1500 mg/day during the last 4 weeks before starting period 0. After period 0 extending over 4 weeks in which period 1000 mg/day **metformin** plus nateglinide placebo are given to the subjects, the subjects are randomised to nateglinide placebo, 60 mg nateglinide or 120 mg nateglinide before main meals for 24 weeks while continuing to receive 1000 mg **metformin** daily.

SUMM

Treatment Group Treatment

- 1 nateglinide placebo\* + 1000 mg **metformin**\*\*
- 2 60 mg nateglinide\* + 1000 mg **metformin**\*\*
- 3 120 mg nateglinide\* + 1000 mg **metformin**\*\*

\*administered before main meals;

\*\*immediately after breakfast and dinner

SUMM . . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** results in a beneficial, especially a synergistic, therapeutic effect, especially on type 2 diabetes, and also in additional benefits such. . .

SUMM . . . beneficial effects are observed in particular with nateglinide. Very good results have been obtained with the combination of nateglinide and **metformin** or **metformin** hydrochloride.

SUMM . . . has to be changed to higher amounts of nateglinide for other reasons. One preferred combination partner in this embodiment is **metformin**.

SUMM . . . that the combination comprises at least two antidiabetic compounds selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin**, or a pharmaceutically acceptable salt thereof.

SUMM Also preferred is a combination in which said other antidiabetic compound is **metformin** or **metformin** hydrochloride or is selected from the group of glitazones, especially rosiglitazone or troglitazone, or in particular, pioglitazone.

SUMM In a very preferred embodiment of the invention nateglinide is administered in combination with **metformin**, **metformin** hydrochloride or a mixture thereof. Nateglinide and **metformin**, **metformin** hydrochloride or a mixture thereof can be administered at different points in time, e.g. nateglinide before breakfast, lunch and dinner and **metformin**, **metformin** hydrochloride or a mixture thereof after breakfast, lunch and dinner, or simultaneously. Preferably, nateglinide and **metformin**, **metformin** hydrochloride or a mixture thereof are administered simultaneously. Very preferably, nateglinide and **metformin**, **metformin** hydrochloride or a mixture thereof are administered thrice daily before breakfast, lunch and dinner. It is also very preferred to administer nateglinide and **metformin**, **metformin** hydrochloride or a mixture thereof together in fixed combination.

SUMM . . . and (ii) and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and

**metformin** or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. In this composition, components (i) and (ii).

SUMM . . . further pharmaceutically active compound e.g. selected from the group consisting of a sulphonyl urea derivative, a pharmaceutically acceptable salt thereof, **metformin** and insulin; or wherein the combined preparation or pharmaceutical composition, respectively, comprises at least one further glitazone or a pharmaceutically.

SUMM . . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** in each case in free form or in form of a pharmaceutically acceptable salt thereof for the preparation of a.

SUMM . . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** in each case in free form or in form of a pharmaceutically acceptable salt thereof for the prevention, delay of.

SUMM . . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin**, is used for the treatment, delay of progression or prevention of one of the diseases, especially metabolic disorders, mentioned herein.

SUMM . . . combination forms. For example, in a two-component combination of, e.g., nateglinide or repaglinide and/or a glitazone as herein defined or **metformin**, treatment with nateglinide or repaglinide can commence prior to, subsequent to or concurrent with commencement of treatment with the glitazone and/or the **metformin**. Furthermore, the term administering also encompasses the use of prodrugs of any of the anti-diabetic drugs that convert in vivo.

SUMM . . . the total weight of the composition. In the case of compositions in accordance with the invention comprising an additional component **metformin**, this will generally be present in an amount of from about 1 to about 90% by weight, more commonly from.

SUMM Especially, the present invention relates to a pharmaceutical composition for combination therapy comprising nateglinide and **metformin** in a pharmaceutical carrier, which is preferably in the form of a tablet, a capsule, a suspension or a liquid.. 130 mg of nateglinide and from about 320 mg to about 1500 mg, more preferably 330 mg to 350 mg, **metformin** per dose unit.

SUMM . . . or repaglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** in an amount which is jointly therapeutically effective against metabolic disorders in which both compounds can also be present in. . . with nateglinide and at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and **metformin** contained in the same dosage unit form. The combination is preferably administered simultaneously.

SUMM . . . least one further pharmaceutically active compound selected from the group consisting of sulphonyl urea derivatives, a pharmaceutically acceptable salt thereof, **metformin** and insulin; or at least one further glitazone, or a pharmaceutically acceptable salt thereof. Preferably, in this method the glitazone.

SUMM . . . least one further pharmaceutically active compound selected from the group consisting of sulphonyl urea derivatives, a pharmaceutically acceptable salt thereof, **metformin** and insulin; or at least one further glitazone or a pharmaceutically acceptable salt thereof. This particular embodiment of the invention. . . to treat post-prandial hyperglycemia. Preferably, the short acting hypoglycemic agent is nateglinide. Also preferably, the long acting

hypoglycemic agent is **metformin**. In an alternate preferred embodiment, the long acting hypoglycemic agent is a glitazone, most preferably 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione; rosiglitazone, pioglitazone, troglitazone, MCC555; . . .

SUMM . . . the daily doses of nateglinde or repaglinide or a pharmaceutically acceptable salt thereof to the glitazone, sulfonyl urea derivative or **metformin** or in each case a pharmaceutically acceptable salt thereof may vary within wide limits especially depending of the nature of. . .

SUMM In one preferred embodiment of the invention the ratio of the daily doses of nateglinde to **metformin** is between 1:3.5 and 1:40, preferably 1:4 and 1:7.1, and very preferably between 1:4.1 and 1:4.5, for example 1:4.2. In a further preferred embodiment of the invention the ratio of the daily doses of nateglinde to **metformin** is between 1:2 and 1:3.

SUMM In one preferred embodiment of the invention the ratio of the daily doses of nateglinde to **metformin** hydrochloride is between 1:1.25 and 1:9, more preferably between 1:2.5 and 1:5, e.g. 1:4.2. In a further preferred embodiment of the invention the ratio of the daily doses of nateglinde to **metformin** hydrochloride is between 4:1 and 1:1, more preferably between 2.5:1 and 1.5:1, e.g. 2:1. In another preferred embodiment of the invention the ratio of the daily doses of nateglinde to **metformin** hydrochloride is between 25:1 and 4.5:1, more preferably between 20:1 and 8:1, in particular 18:1, 16:1, 14:1, 10:1 and especially. . .

SUMM In one preferred embodiment, the active ingredient is **metformin**, the warm-blooded animal being is a human of about 70 kg body weight and the dosage of said compound is. . . 1500, mg/day, per adult patient. In one preferred embodiment of the invention, 180 mg of nateglinide and 750 mg of **metformin** are given as a daily dose to a human patient of about 70 kg body weight. In a further preferred embodiment of the invention, the active ingredient **metformin** shall be applied in the form of **metformin** hydrochloride in a dosage between 1500 and 3000, especially 1500, 1700 or 2550 mg/day to a warm-blooded animal of about 70 kg body weight. In another preferred embodiment, the active ingredient **metformin** shall be applied in the form of **metformin** hydrochloride in a dosage between 700 and 1250, especially between 750 and 1100, e.g. 1000, mg/day to a warm-blooded animal. . .

SUMM . . . to 3500, more preferably 250 to 3000, for example 500, 1000, 1500, 2000, 2500, mg/day. If the sulfonyl urea derivative **glimepiride** is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the. . .

SUMM The preparation of **metformin** (dimethyldiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James. . .

IT 557-04-0 657-24-9, Metformin 1115-70-4, Metformin hydrochloride 9003-39-8, Povidone 9004-10-8, Insulin, biological studies 64044-51-5, Lactose monohydrate 74811-65-7, Croscarmellose sodium 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 135062-02-1, Repaglinide  
(pharmaceuticals contg. nateglinide or repaglinide for treating diabetes or conditions assocd. with diabetes)

L9 ANSWER 7 OF 27 USPATFULL on STN  
AN 2003:106732 USPATFULL  
TI Combinations comprising a beta-agonist and a further antidiabetic agent  
IN Sanders Arch, Jonathan Robert, Welwyn Garden City, UNITED KINGDOM  
PA SmithKline Beecham p.l.c. (non-U.S. corporation)  
PI US 2003073644 A1 20030417  
AI US 2002-243164 A1 20020913 (10)

RLI Continuation of Ser. No. US 2001-831651, filed on 11 Jul 2001, ABANDONED  
A 371 of International Ser. No. WO 1999-GB3755, filed on 11 Nov 1999,  
UNKNOWN

PRAI GB 1998-24789 19981111  
GB 1998-24791 19981111  
GB 1998-24790 19981111

DT Utility  
FS APPLICATION

LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW 2220, P.O. Box  
1539, King of Prussia, PA, 19406-0939

CLMN Number of Claims: 18  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 769

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment of diabetes mellitus and conditions  
associated with diabetes mellitus in a mammal such as a human, which  
method comprises administering an effective, non-toxic and  
pharmaceutically acceptable amount of a beta agonist and another  
antidiabetic agent, to a mammal in need thereof.

SUMM . . . in the treatment of Type 2 diabetes. Acarbose, voglibose,  
emiglitate and miglitol are examples of alpha glucosidase inhibitors.  
1,1-Dimethylbiguanidine (or **metformin**) is a particular example  
of a biguanide.

SUMM . . . agents and are used in the treatment of Type 2 diabetes.  
Examples of sulphonylureas include glibenclamide (or glyburide),  
glipizide, gliclazide, **glimepiride**, tolazamide and  
tolbutamide.

DETD [0023] Suitable biguanides include **metformin**, buformin or  
phenformin, especially **metformin**.

DETD [0025] Suitable sulphonylureas include glibenclamide, glipizide,  
gliclazide, **glimepiride**, tolazamide and tolbutamide. Further  
sulphonylureas include acetohexamide, carbutamide, chlorpropamide,  
glibomuride, gliquidone, glisentide, glisolamide, glisoxepide,  
glyclopamide and glycylamide. Also included is. . .

DETD [0168] For the biguanide, a suitable dosage of **metformin** is  
between 100 to 3000 mg, for example 250, 500 mg, 850 mg or 1000 mg.

DETD . . . a suitable amount of gliquidone is in the range of from 15 to  
180 mg. Also a suitable amount of **glimepiride** is 1 to 6mg and  
a suitable amount of glipentide is 2.5 to 20 mg.

CLM What is claimed is:  
6. A method according to claim 5, wherein the biguanide is selected from  
**metformin**, buformin and phenformin.

9. A method according to claim 7 or claim 8, wherein the sulphonylurea  
is selected from glibenclamide, glipizide, gliclazide,  
**glimepiride**, tolazamide, tolbutamide, acetohexamide,  
carbutamide, chlorpropamide, glibomuride, gliquidone, glisentide,  
glisolamide, glisoxepide, glyclopamide, glycylamide and glipentide.

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2,  
Chlorpropamide 114-86-3, Phenformin 339-43-5, Carbutamide 631-27-6,  
Glyclopamide 657-24-9, Metformin 664-95-9, Glycylamide 692-13-7,  
Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 10238-21-8,  
Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide  
25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9,  
Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 56180-94-0,  
Acarbose 72432-03-2, Miglitol 74772-77-3, Ciglitazone 74772-77-3D,  
Ciglitazone, derivs. 80879-63-6, Emiglitate 83480-29-9, Voglibose  
93479-97-1, Glimepiride 97322-87-7, Troglitazone 97322-87-7D,  
Troglitazone, derivs. 109229-58-5, Englitzazone 109229-58-5D,  
Englitzazone, derivs. 111025-46-8, Pioglitazone 111025-46-8D,

Pioglitazone, derivs. **122320-73-4 122320-73-4D**,  
 derivs. 193759-90-9 193759-94-3 193759-96-5 193759-98-7  
 193760-02-0 193760-04-2 193760-06-4 193760-08-6 193760-13-3  
 193760-25-7 193760-28-0 193760-31-5 193760-41-7 193760-43-9  
 193760-55-3 193760-59-7 193760-63-3 193760-81-5 193760-89-3  
 193760-93-9 193761-11-4 193761-29-4 193761-31-8 193761-36-3  
 268727-70-4 268727-71-5 268727-72-6 268727-73-7 268727-74-8  
 268727-75-9 268727-76-0 268727-77-1 268727-78-2 268727-79-3  
 268727-80-6 268727-81-7 268727-82-8 268727-83-9 268727-84-0  
 268727-85-1 268727-86-2 268727-88-4 268727-89-5 268727-90-8  
 268727-91-9 268727-92-0 268727-93-1 268727-94-2 268727-95-3  
 268727-96-4 268727-97-5 268727-98-6 268727-99-7 268728-00-3  
 268728-01-4 268728-02-5 268728-03-6 268728-04-7 268728-05-8  
 268728-06-9 268728-07-0 268728-08-1 268728-09-2 268728-10-5  
 268728-11-6 268728-12-7 268728-13-8 268728-14-9 268728-15-0  
 268728-16-1 268728-17-2 268728-18-3 268728-19-4 268728-20-7  
 268728-21-8 268728-22-9 268728-23-0 268728-24-1 268728-25-2  
 268728-26-3 268728-27-4 268728-28-5 268728-29-6 268728-30-9  
 268728-31-0 268728-32-1 268728-33-2 268728-34-3 268728-35-4  
 268728-36-5 268728-37-6 268728-38-7 268728-39-8 268728-40-1  
 (.beta.-agonist-antidiabetic combination for treatment of diabetes  
 mellitus and conditions assocd. with diabetes)

L9 ANSWER 8 OF 27 USPATFULL on STN  
 AN 2003:93574 USPATFULL  
 TI Amino acid complexes of C-aryl glucosides for treatment of diabetes and  
 method  
 IN Gougoutas, Jack Z., Princeton, NJ, UNITED STATES  
 PI US 2003064935 A1 20030403  
 AI US 2002-117914 A1 20020408 (10)  
 PRAI US 2001-283097P 20010411 (60)  
 DT Utility  
 FS APPLICATION  
 LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O  
 BOX 4000, PRINCETON, NJ, 08543-4000  
 CLMN Number of Claims: 19  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 1995  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB Crystalline complexes are obtained from a 1:1 or 2:1 mixtures of either  
 the (D) or (L) enantiomer of natural amino acids and compounds of  
 formula ##STR1##

wherein

R.sup.1, R.sup.2 and R.sup.2a are independently hydrogen, OH, OR.sup.5,  
 alkyl, --OCHF.sub.2, --OCF.sub.3, --SR.sup.5a or halogen;

R.sup.3 and R.sup.4 are independently hydrogen, OH, OR.sup.5b, alkyl,  
 cycloalkyl, CF.sub.3, --OCHF.sub.2, --OCF.sub.3, halogen,  
 --CONR.sup.6R.sup.6a, --CO.sub.2R.sup.5c, --CO.sub.2H, --COR.sup.6b,  
 --CH(OH)R.sup.6c, --CH(OR.sup.5d)R.sup.6d, --CN, --NHCOR.sup.5e,  
 --NHSO.sub.2R.sup.5f, --NHSO.sub.2Aryl, --SR.sup.5g, --SOR.sup.5h,  
 --SO.sub.2R.sup.5i, or a five, six or seven membered heterocycle which  
 may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or  
 SO.sub.2, or R.sup.3 and R.sup.4 together with the carbons to which they  
 are attached form an annelated five, six or seven membered carbocycle or  
 heterocycle which may contain 1 to 4 heteroatoms in the ring which are  
 N, O, S, SO, and/or SO.sub.2;

R.sup.5, R.sup.5a, R.sup.5b, R.sup.5c, R.sup.5d, R.sup.5e, R.sup.5f,

R.sup.5g, R.sup.5h and R.sup.5i are independently alkyl;

R.sup.6, R.sup.6a, R.sup.6b, R.sup.6c and R.sup.6d are independently hydrogen, alkyl, aryl, alkylaryl or cycloalkyl, or R.sup.6 and R.sup.6a together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO.sub.2.

A method is also provided for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above complex alone or in combination with another antidiabetic agent or other therapeutic agent.

SUMM [0130] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin HCl**.

SUMM [0132] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0140] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0141] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:

10. The combination as defined in claim 9 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide,. . .

IT 51-64-9, Dexamphetamine 94-20-2, Chlorpropamide 122-09-8, Phentermine 637-07-0, Clofibrate 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 141750-63-2, Nisvastatin 141758-74-9, AC2993 144288-97-1, TS 962 145599-86-6, Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427 159183-92-3, L750355 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 287714-41-4, Rosuvastatin 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544 335149-23-0, NVPDPP-728A 335149-24-1, ATL-962 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipiride 430433-39-9, Isaglitazone (prepn. of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

L9 ANSWER 9 OF 27 USPATFULL on STN  
AN 2003:86880 USPATFULL  
TI Drug comprising combination  
IN Sugiyama, Yasuo, Kawanishi-shi, Hyogo, JAPAN  
Odaka, Hiroyuki, Kobe-shi, Hyogo, JAPAN

Naruo, Ken-ichi, Sanda-shi, Hyogo, JAPAN

PI US 2003060488 A1 20030327

AI US 2002-203300 A1 20020809 (10)

WO 2001-JP880 20010208

PRAI JP 2000-38265 20000210

DT Utility

FS APPLICATION

LREP WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800,  
WASHINGTON, DC, 20006-1021

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1215

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A TNF-.alpha. inhibitor comprising an insulin sensitizer in combination  
with an HMG-CoA reductase inhibitor is useful as an agent for the  
prophylaxis or treatment of an inflammatory disease and the like.

SUMM . . . glycopyramide and ammonium salt thereof, glibenclamide,  
gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibornuride,  
glipizide, gliquidone, glisoxepide, glybuthiazole, glybuzole,  
glyhexamide, glymidine, glypinamide, phenbutamide, tolcyclamide,  
**glimepiride** and the like.

SUMM [0183] The biguanides are exemplified by phenformin, **metformin**  
, buformin and the like.

IT 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0,  
Pravastatin 93957-54-1, Fluvastatin 111025-46-8, Pioglitazone  
**122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin  
145599-86-6, Cerivastatin 147098-20-2, ZD-4522 147511-69-1,  
Itavastatin  
(TNF-.alpha. inhibitors contg. combination of insulin  
resistance-ameliorating agents with HMG-CoA reductase inhibitors)

L9 ANSWER 10 OF 27 USPATFULL on STN

AN 2003:65429 USPATFULL

TI Combination therapy comprising glucose reabsorption inhibitors and PPAR  
modulators

IN Bussolari, Jacqueline C., Skillman, NJ, UNITED STATES  
Chen, Xiaoli, Belle Mead, NJ, UNITED STATES  
Conway, Bruce R., Doylestown, PA, UNITED STATES  
Demarest, Keith T., Flemington, NJ, UNITED STATES  
Ross, Hamish N.M., Far Hills, NJ, UNITED STATES  
Severino, Rafael, Madrid, SPAIN

PI US 2003045553 A1 20030306

AI US 2002-115827 A1 20020403 (10)

PRAI US 2001-281429P 20010404 (60)

DT Utility

FS APPLICATION

LREP AUDLEY A. CIAMPORCERO JR., JOHNSON & JOHNSON, ONE JOHNSON & JOHNSON  
PLAZA, NEW BRUNSWICK, NJ, 08933-7003

CLMN Number of Claims: 67

ECL Exemplary Claim: 1

DRWN 7 Drawing Page(s)

LN.CNT 2106

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combination therapy comprising PPAR modulators and glucose reabsorption  
inhibitors useful for the treatment of diabetes and Syndrome X are  
disclosed.

SUMM . . . may be higher than normal but not at the diabetes diagnostic  
criterion, is treated in some countries (e.g., Germany) with  
**metformin** to prevent diabetes. The anti-diabetic agents may be  
combined with pharmacological agents for the treatment of the  
concomitant co-morbidities (e.g.,. . .

SUMM [0010] First-line therapies typically include **metformin** and sulfonylureas as well as thiazolidinediones. **Metformin** monotherapy is a first line choice, particularly for treating type II diabetic patients who are also obese and/or dyslipidemic. Lack of an appropriate response to **metformin** is often followed by treatment with **metformin** in combination with sulfonylureas, thiazolidinediones, or insulin. Sulfonylurea monotherapy (including all generations of drugs) is also a common first line. . . .

DETD [0209] (C) Biguanides, which decrease liver glucose production and increases the uptake of glucose. Examples include **metformin** such as:

DETD [0210] (1) 1,1-dimethylbiguanide (e.g., **Metformin**-DepoMed, **Metformin**-Biovail Corporation, or **METFORMIN** GR ( **metformin** gastric retention polymer)); and

DETD [0211] (2) **metformin** hydrochloride (N,N-dimethylimidododicarbonimidic diamide monohydrochloride, also known as LA 6023, BMS 207 150, GLUCOPHAGE, or GLUCOPHAGE XR.

DETD [0265] (5f) **glimepiride** (1H-pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-, trans-, also known as Hoe-490 or AMARYL);

DETD [0359] 4. UK Prospective Diabetes Study Group. (1998) Effect of intensive blood glucose control with **metformin** on complications in overweight pateints with type 2 diabetes. Lancet 352: 854-865.

IT 2295-31-0D, Thiazolidinedione, analogs 9004-10-8D, Insulin, analogs 23141-09-5D, derivs. 33321-31-2 49562-28-9, Fenofibrate 79714-31-1, Risarestat 97322-87-7, Troglitazone 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 130542-74-4D, derivs. 153559-49-0, Bexarotene 170861-63-9, JT 501 174456-32-7D, derivs. 196808-45-4, Farglitazar 199113-98-9, Nn2344 199914-96-0, YM440 209746-56-5D, derivs. 209746-59-8, T-1095 213252-19-8, KRP-297 222834-21-1, NN 622 251565-85-2, AR-H 039242 430433-39-9, Isaglitazone 469886-17-7D, derivs.

(combination therapy comprising glucose reabsorption inhibitors and PPAR modulators)

L9 ANSWER 11 OF 27 USPATFULL on STN

AN 2003:57950 USPATFULL

TI Pyrazinone inhibitors of fatty acid binding protein and method

IN Sulsky, Richard, West Trenton, NJ, UNITED STATES

Robl, Jeffrey A., Newtown, PA, UNITED STATES

PI US 2003040516 A1 20030227

AI US 2002-194028 A1 20020712 (10)

PRAI US 2001-305356P 20010713 (60)

DT Utility

FS APPLICATION

LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1434

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB aP2 inhibiting compounds are provided having the formula ##STR1##

wherein A, X, R and Z are as described herein.

A method is also provided for treating diabetes and related diseases, especially Type II diabetes, employing such aP2 inhibitors alone or in combination with other therapeutic agents, including other antidiabetic agent such as **metformin**, glyburide, troglitazone and/or

insulin.

AB . . . II diabetes, employing such  $\alpha$ 2 inhibitors alone or in combination with other therapeutic agents, including other antidiabetic agent such as **metformin**, glyburide, troglitazone and/or insulin.

SUMM [0139] The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

SUMM [0141] The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0149] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0150] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:  
13. The pharmaceutical composition of claim 12 wherein the antidiabetic agents are selected from **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, rosiglitazone, piaglitazone, insulin, and **metformin**/glyburide combinations.

IT 94-20-2, Chlorpropamide 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 21187-98-4, Gliclazide 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 93479-97-1, Glimepiride 97322-87-7, Troglitazone 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 430433-17-3, Glipiride  
(combination of pyrazinone inhibitor of fatty acid binding protein and another drug)

L9 ANSWER 12 OF 27 USPATFULL on STN

AN 2003:24218 USPATFULL

TI Novel remedies with the use of beta 3 agonist

IN Ogawa, Kohei, Shizuoka, JAPAN  
Umeno, Hiroshi, Shizuoka, JAPAN

PI US 2003018061 A1 20030123

AI US 2002-182375 A1 20020729 (10)  
WO 2001-JP553 20010126

PRAI JP 2000-20733 20000128

DT Utility

FS APPLICATION

LREP YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1675

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided is a therapeutic agent comprising at least one member selected from the group consisting of an anticholinergic agent, a monoamine reuptake inhibitor, a lipase inhibitor, a selective serotonin reuptake inhibitor, insulin, an insulin secretagogue, biguanide, an .alpha.-glucosidase inhibitor, an insulin resistance improving agent, a HMG-CoA reductase inhibitor, an anion exchange resin, a clofibrate type drug and a nicotinic acid type drug, and a compound having a .beta.3 agonist activity. The .beta.3-agonist has an activity of inhibiting dysuria. Further, when used together with a remedy for dysuria such as

propiverine, oxybutynin hydrochloride or tolterodine, it exerts an enhanced anti-dysuria effect. When used together with an antiobestic agent such as sibutramine or orlistat, it exerts an enhanced antiobestic effect. When used together with an antidiabetic agent such as insulin, glibenclamide, acarbose or rosiglitazone, it exerts an enhanced antidiabetic effect. When used together with an antilipemic agent such as bezafibrate or pravastatin, it exerts an enhanced antilipemic effect.

SUMM . . . and an insulin resistance improving agent are used. As compounds having an effect that promotes insulin secretion, glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, chlorpropamide, glycopyramide, and meglitinide are used. Further, compounds called repaglinide and nateglinide have begun to be used, . . . secretagogues have side effects of appetite promotion and hypoglycemia, and the situation is not necessarily a satisfactory one. As biguanide, **metformin** and buformin are used, and they are known to cause lactic acidosis (IGAKU NO AYUMI, Diabetes Mellitus, Vol. 188, p504-509. . . .

SUMM . . . promotes insulin secretion from .beta. cells by stimulating K.sub.ATP channels of pancreatic .beta.-cells. Specific examples thereof include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, chlorpropamide, glycopyramide, meglitinide, repaglinide, nateglinide and mitiglinide, and in particular, repaglinide, nateglinide and mitiglinide are preferred examples.

SUMM [0109] Examples of a Biguanide Include **Metformin**, and Buformin

CLM What is claimed is:

17. The therapeutic agent of claim 14 or 16, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, chlorpropamide, glycopyramide, meglitinide, repaglinide, nateglinide or mitiglinide.

21. The therapeutic agent of claim 14 or 20, wherein the biguanide is **metformin** or buformin.

IT 56-03-1D, Biguanide, derivs. 59-67-6, Nicotinic acid, biological studies 637-07-0, Clofibrate 1508-65-2, Oxybutynin hydrochloride 9004-10-8, Insulin, biological studies 10238-21-8, Glibenclamide 41859-67-0, Bezafibrate 56180-94-0, Acarbose 60569-19-9, Propiverine 81093-37-0, Pravastatin 97322-87-7, Troglitazone 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 124937-51-5, Tolterodine 161600-01-7, MCC 555 170861-63-9, JTT 501 193760-08-6 213252-19-8, KRP 297 268727-76-0 268728-01-4 268728-06-9 268728-13-8 274687-78-4, GI 262570 333754-68-0 352194-77-5 (novel remedies with the use of .beta.3 agonists as antidiabetics and antilipidemics and for treatment of urination disorder)

L9 ANSWER 13 OF 27 USPATFULL on STN

AN 2003:4123 USPATFULL

TI Use of glycogen phosphorylase inhibitors

IN Treadway, Judith L., Mystic, CT, UNITED STATES

PI US 2003004162 A1 20030102

AI US 2001-813335 A1 20010320 (9)

PRAI US 2000-191381P 20000322 (60)

DT Utility

FS APPLICATION

LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159,, Eastern Point Road, Groton, CT, 06340

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 4011

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods of treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods comprise administering to an individual in need thereof an effective amount of a glycogen phosphorylase inhibitor; effective amounts of a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic agent; or effective amounts of a glycogen phosphorylase inhibitor and an anti-obesity agent.

The invention further provides methods of treating prophylactically an individual in whom Type 2 diabetes mellitus has not yet presented, but in whom there is an increased risk of developing such condition, which methods comprise administering to an individual in need thereof a pharmaceutical composition comprising effective amounts of a glycogen phosphorylase inhibitor and a non-glycogen phosphorylase inhibiting anti-diabetic agent; or effective amounts of a glycogen phosphorylase inhibitor and an anti-obesity agent.

DETD . . . and analogs thereof useful in the methods of the invention may comprise, for example, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glipizide, **glimepiride**, repaglinide, and meglitinide. Preferred biguanides useful in the methods of the invention may comprise, for example, **metformin**, phenformin, and buformin. Preferred .alpha..sub.2-antagonists and imidazolines useful in the methods of the invention may comprise, for example, midaglizole, isaglidole, . . .

CLM What is claimed is:

. . . MX 6054; said sulfonylurea or analog thereof is selected from the group consisting of chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glipizide, **glimepiride**, repaglinide, and meglitinide; said biguanide is selected from the group consisting of **metformin**, phenformin, and buformin; said .alpha..sub.2-antagonist or imidazoline is selected from the group consisting of midaglazole, isaglidole, deriglidole, idazoxan, efaroxan, and. . .

IT 53-43-0, Dehydroepiandrosterone 59-67-6, Nicotinic acid, biological studies 64-77-7, Tolbutamide 90-82-4, Pseudoephedrine 94-20-2, Chlorpropamide 114-86-3, Phenformin 122-09-8, Phentermine 299-42-3, Ephedrine 458-24-2, Fenfluramine 504-75-6, Imidazoline 657-24-9, Metformin 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 3239-44-9, Dexfenfluramine 9001-39-2, Glucose-6-phosphatase 9004-10-8, Insulin, biological studies 10238-21-8, Glibenclamide 14838-15-4, Phenylpropanolamine 23602-78-0, Benfluorex 25614-03-3, Bromocriptine 27686-84-6, Masoprocol 29094-61-9, Glipizide 51037-30-0, Acipimox 54870-28-9, Meglitinide 56180-94-0, Acarbose 68367-52-2, Sorbinil 72432-03-2, Miglitol 74772-77-3, Ciglitazone 75358-37-1, Linoglitride 78860-34-1, L-783281 79944-58-4, Idazoxan 80879-63-6, Emiglitide 82159-09-9, Epalrestat 82964-04-3, Tolrestat 83480-29-9, Voglibose 86615-96-5, BRL-35135 88431-47-4, Clomoxir 89197-32-0, Efaroxan 89750-14-1, Glucagon-like peptide I 90730-96-4, BRL-37344 93479-97-1, Glimepiride 96829-58-2, Orlistat 97322-87-7, Troglitazone 105182-45-4, Fluparoxan 105816-04-4, A-4166 106650-56-0, Sibutramine 109229-58-5, Englitazone 110605-64-6, Isaglidole 110703-94-1, Zopolrestat 111025-46-8, Pioglitazone 112733-06-9, Zenarestat 118549-37-4, Insulinotropin **122320-73-4**, Rosiglitazone 122575-28-4, Naglivan 122830-14-2, Deriglidole 124083-20-1, Etomoxir 127214-23-7, Camiglibose 130714-47-5, WAG 994 135062-02-1, Repaglinide 138908-40-4, CL 316243 141200-24-0, Darglitazone 141732-76-5, exendin-4 151126-32-8, Pramlintide 161600-01-7, MCC-555 161748-40-9, BTS-67582 169494-85-3, Leptin 170861-63-9, JTT-501 187887-46-3, AC-137 (pharmaceutical in combination with; synthesis of indolyl-amides as

reach maximum **metformin**-plasma concentration (Tmax) by at least about 30% (relative to marketed rapid-release **metformin** formulations), while having an insignificant effect on area under the plasma-**metformin** concentration time curve (AUC) and % urinary recovery (UR) of the dose of **metformin** (relative to marketed rapid-release **metformin** formulations).

IT 59-67-6, Nicotinic acid, biological studies 657-24-9, Metformin 657-24-9D, Metformin, salts 943-45-3D, Fibric acid, derivs. 1115-70-4, Metformin hydrochloride 9004-10-8, Insulin, biological studies 9004-32-4, Sodium carboxymethyl cellulose 9004-57-3, Ethyl cellulose 9004-65-3, Hydroxypropyl methyl cellulose 9005-38-3, Sodium alginate 9050-04-8, Calcium carboxymethyl cellulose 10238-21-8, Glyburide 29094-61-9, Glipizide 31566-31-1, Glycerylmonostearate 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 89750-14-1, Glucagon-like peptide I 93957-54-1, Fluvastatin 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin 145599-86-6, Cerivastatin (biphasic controlled-release delivery systems for high soly. pharmaceuticals)

L9 ANSWER 16 OF 27 USPATFULL on STN

AN 2002:251945 USPATFULL

TI C-aryl glucoside SGLT2 inhibitors and method

IN Ellsworth, Bruce, Princeton, NJ, UNITED STATES

Washburn, William N., Titusville, NJ, UNITED STATES

Sher, Philip M., Plainsboro, NJ, UNITED STATES

Wu, Gang, Princeton, NJ, UNITED STATES

Meng, Wei, Pennington, NJ, UNITED STATES

PI US 2002137903 A1 20020926

US 6515117 B2 20030204

AI US 2002-151436 A1 20020520 (10)

RLI Continuation-in-part of Ser. No. US 2000-679027, filed on 4 Oct 2000,

GRANTED, Pat. No. US 6414126

PRAI US 2000-194615P 20000405 (60)

US 1999-158773P 19991012 (60)

DT Utility

FS APPLICATION

LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O

BOX 4000, PRINCETON, NJ, 08543-4000

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1148

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An SGLT2 inhibiting compound is provided having the formula ##STR1##

A method is also provided for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above compound alone or in combination with another antidiabetic agent or other therapeutic agent.

SUMM . . . novel, safe, and orally active antidiabetic agents is also desired in order to complement existing therapies, including the sulfonylureas, thiazolidinediones, **metformin**, and insulin, and to avoid the potential side effects associated with the use of these other agents.

SUMM [0114] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

SUMM [0116] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0124] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipyrizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0125] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:  
 7. The combination as defined in claim 6 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipyrizide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, . . .

IT 51-64-9, Dexamphetamine 94-20-2, Chlorpropamide 122-09-8, Phentermine 637-07-0, Clofibrate 657-24-9, Metformin 943-45-3D, Fibric acid, derivs. 9004-10-8, Insulin, biological studies 9077-14-9, Squalene synthetase 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol. 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 37250-24-1, HMG CoA reductase 49562-28-9, Fenofibrate 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone **122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 141750-63-2, Nisvastatin 141758-74-9, AC2993 144288-97-1, TS 962 145599-86-6, Cerivastatin 152755-31-2, LY295427. 159183-92-3, L750355 161600-01-7, Isaglitazone 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 287714-41-4, Rosuvastatin 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544 335149-23-0, NVPDPP-728A 335149-24-1, ATL-962 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipyrizide  
 (prepn. of antidiabetic agents C-aryl glucosides as human SGLT2 inhibitors)

L9 ANSWER 17 OF 27 USPATFULL on STN

AN 2002:179187 USPATFULL

TI HMG-CoA reductase inhibitors and method

IN Robl, Jeffrey A., Newtown, PA, UNITED STATES  
 Chen, Bang-Chi, Plainsboro, NJ, UNITED STATES  
 Sun, Chong-Qing, East Windsor, NJ, UNITED STATES

PI US 2002094977 A1 20020718

AI US 2001-7407 A1 20011204 (10)

RLI Continuation-in-part of Ser. No. US 2001-875155, filed on 6 Jun 2001, PENDING

PRAI US 2000-211595P 20000615 (60)

DT Utility

FS APPLICATION

LREP Stephen B. Davis, Bristol-Myers Squibb Company, Patent Department, P.O. Box 4000, Princeton, NJ, 08543-4000

CLMN Number of Claims: 49

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2539

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing

HDL cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis ##STR1##

and pharmaceutically acceptable salts thereof, wherein X is O, S, SO, SO.sub.2 or NR.sub.7;

Z is ##STR2##

n is 0 or 1;

R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; and

R.sub.3 to R.sub.10 are as defined herein.

SUMM [0228] The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

SUMM [0230] The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0238] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0239] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:

25. The combination as defined in claim 24 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide,. . .

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-01-7, Spironolactone 52-53-9, Verapamil 54-31-9, Furosemide 58-32-2, Dipyrindamole 58-93-5, Hydrochlorothiazide 59-67-6, Niacin, biological studies 94-20-2, Chlorpropamide 122-09-8, Phentermine 525-66-6, Propranolol 564-25-0, Doxycycline 637-07-0, Clofibrate 657-24-9, Metformin 1684-40-8, Tacrine hydrochloride 3416-24-8, Glucosamine 4205-91-8, Clonidine hydrochloride 9004-61-9, Hyaluronic acid 9007-28-7, Chondroitin sulfate 10118-90-8, Minocycline 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 19237-84-4, Prazosin hydrochloride 21187-98-4, Gliclazide 21829-25-4, Nifedipine 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 26807-65-8, Indapamide 29094-61-9, Glipizide 29122-68-7, Atenolol 42200-33-9, Nadolol 49562-28-9, Fenofibrate 55142-85-3, Ticlopidine 56180-94-0, Acarbose 56211-40-6, Torasemide 62571-86-2, Captopril 68475-42-3, Anagrelide 72432-03-2, Miglitol 72956-09-3, Carvedilol 75330-75-5, Lovastatin 75847-73-3, Enalapril 76547-98-3, Lisinopril 79902-63-9, Simvastatin 80830-42-8, Fentiapril 81093-37-0, Pravastatin 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril 89750-14-1, Glucagon-like peptide I 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 98048-97-6, Fosinopril 103775-10-6, Moexipril 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 113665-84-2, Clopidogrel 114798-26-4, Losartan 120014-06-4, Donepezil 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6,

Irbesartan 141758-74-9, AC2993 143443-90-7, Ifetroban 143653-53-6,  
 Abciximab 144288-97-1, TS 962 144494-65-5, Tirofiban 145599-86-6,  
 Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427  
 159183-92-3, 1750355 160135-92-2, Gemopatrilat 161600-01-7,  
 Isaglitazone 162011-90-7, Vioxx 166518-60-1, Avasimibe 167305-00-2,  
 Omapatrilat 169319-62-4, CGS 30440 169590-42-5, Celebrex  
 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700  
 182815-44-7, Cholestagel 188627-80-7, Eptifibatide 196808-45-4,  
 GI-262570 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8,  
 KRP297 244081-42-3, AJ9677 246852-12-0, Amlodipine mesylate  
 251572-86-8, P32/98 287714-41-4, Rosuvastatin 335149-08-1, L895645  
 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, AR-HO39242  
 335149-19-4, GW-409544 335149-23-0, NVP-DPP-728A 335149-24-1, ATL-962  
 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipyrside  
 430433-43-5, CP644673

(coadministered agents; prepn. of benzoxepinopyridines as HMG-CoA  
 reductase inhibitors for treatment of hyperlipidemia,  
 hypercholesterolemia, hypertriglyceridemia, atherosclerosis, and other  
 disorders)

L9 ANSWER 18 OF 27 USPATFULL on STN  
 AN 2002:165255 USPATFULL  
 TI Pharmaceutical composition  
 IN Odaka, Hiroyuki, Hyogo, JAPAN  
 Yamane, Masahiro, Osaka, JAPAN  
 PI US 2002086885 A1 20020704  
 AI US 2001-36208 A1 20011229 (10)  
 RLI Division of Ser. No. US 1999-380059, filed on 25 Aug 1999, PATENTED A  
 371 of International Ser. No. WO 1999-JP3496, filed on 29 Jun 1999,  
 UNKNOWN  
 PRAI JP 1998-183700 19980630  
 DT Utility  
 FS APPLICATION  
 LREP TAKEDA PHARMACEUTICALS NORTH AMERICA, INC, INTELLECTUAL PROPERTY  
 DEPARTMENT, 475 HALF DAY ROAD, SUITE 500, LINCOLNSHIRE, IL, 60069  
 CLMN Number of Claims: 21  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 1160  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB A pharmaceutical composition which comprises an insulin sensitizer in  
 combination with an anorectic, which is useful as an agent for  
 preventing or treating diabetes.  
 SUMM . . . glycopyramide or its ammonium salt, glibenclamide, gliclazide,  
 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide,  
 gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide,  
 glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride  
 , etc.  
 SUMM [0189] Examples of the biguanides include phenformin, metformin  
 , buformin, etc.  
 IT 97322-87-7, Troglitazone 122820-73-4, Rosiglitazone  
 155141-29-0, Rosiglitazone maleate 170861-63-9  
 (insulin sensitizer in combination with an anorectic for the treatment  
 of diabetes)

L9 ANSWER 19 OF 27 USPATFULL on STN  
 AN 2002:149184 USPATFULL  
 TI Pyridone inhibitors of fatty acid binding protein and method  
 IN Sulsky, Richard, West Trenton, NJ, UNITED STATES  
 Robl, Jeffrey A., Newtown, PA, UNITED STATES  
 PI US 2002077340 A1 20020620  
 AI US 2001-989212 A1 20011120 (9)

PRAI US 2000-252014P 20001120 (60)  
DT Utility  
FS APPLICATION  
LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O  
BOX 4000, PRINCETON, NJ, 08543-4000  
CLMN Number of Claims: 18  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1335  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Compounds are provided having the formula ##STR1##

wherein A, Q, and X are as described herein.

A method is also provided for treating diabetes and related diseases, especially Type II diabetes, employing such compounds alone or in combination with other antidiabetic agents such as **metformin**, glyburide, troglitazone and/or insulin.

AB . . . and related diseases, especially Type II diabetes, employing such compounds alone or in combination with other antidiabetic agents such as **metformin**, glyburide, troglitazone and/or insulin.

SUMM [0114] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

SUMM [0116] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0124] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0125] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:  
15. The combination of claim 14 wherein the antidiabetic agent is **metformin**, glyburide, **glimepiride**, glipiride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, rosiglitazone, and/or insulin.

IT 56-03-1D, Biguanide, derivs. 94-20-2, Chlorpropamide 657-24-9, Metformin 2295-31-0D, Thiazolidinedione, derivs. 10238-21-8, Glyburide 21187-98-4, Gliclazide 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 93479-97-1, Glimepiride 97322-87-7, Troglitazone 106612-94-6 **122320-73-4**, Rosiglitazone (antidiabetic combination therapy agent; prepn. and use of pyridone aP2 inhibitors in combination therapy with other antidiabetic agents for treatment of Type II diabetes and related diseases)

L9 ANSWER 20 OF 27 USPATFULL on STN

AN 2002:119913 USPATFULL

TI HMG-CoA reductase inhibitors and method

IN Robl, Jeffrey A., Newtown, PA, UNITED STATES

Chen, Bang-Chi, Plainsboro, NJ, UNITED STATES

Sun, Chong-Qing, East Windsor, NJ, UNITED STATES

PI US 2002061901 A1 20020523

AI US 2001-8154 A1 20011204 (10)

RLI Continuation-in-part of Ser. No. US 2001-875218, filed on 6 Jun 2001, PENDING

PRAI US 2000-211594P 20000615 (60)

DT Utility  
FS APPLICATION  
LREP STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000  
CLMN Number of Claims: 45  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 2458  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis as well as Alzheimer's disease and osteoporosis  
##STR1##

and pharmaceutically acceptable salts thereof, ##STR2##

n is 0 or 1;

x is 0, 1, 2, 3 or 4;

y is 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0; and optionally one or more carbons of (CH.sub.2).sub.x and/or (CH.sub.2).sub.y together with additional carbons form a 3 to 7 membered spirocyclic ring;

R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R.sub.3 is H or lower alkyl;

R.sub.4 and R.sub.7 are as defined herein.

SUMM [0225] The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as **metformin** or phenformin or salts thereof, preferably **metformin** HCl.

SUMM [0227] The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), **glimepiride** (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on. . .

SUMM [0235] Where present, **metformin**, the sulfonyl ureas, such as glyburide, **glimepiride**, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may. . .

SUMM [0236] Where present, **metformin** or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day. . .

CLM What is claimed is:  
21. The combination as defined in claim 20 wherein the antidiabetic agent is 1, 2, 3 or more of **metformin**, glyburide, **glimepiride**, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GL-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide,. . .

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-01-7, Spironolactone 52-53-9, Verapamil 54-31-9, Furosemide 58-32-2, Dipyrindamole 58-93-5, Hydrochlorothiazide 59-67-6, Nicotinic acid, biological studies 59-67-6D, Nicotinic acid, derivs. 94-20-2, Chlorpropamide 122-09-8, Phentermine 303-98-0, Coenzyme Q10 525-66-6, Propranolol

564-25-0, Doxycycline 637-07-0, Clofibrate 657-24-9, Metformin  
 943-45-3D, Fibric acid, derivs. 1684-40-8, Tacrine hydrochloride  
 3416-24-8, Glucosamine 4205-91-8, Clonidine hydrochloride 9002-64-6,  
 Parathyroid hormone 9004-10-8, Insulin, biological studies 9004-61-9,  
 Hyaluronic acid 9007-28-7, Chondroitin sulfate 10118-90-8,  
 Minocycline 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine  
 19237-84-4, Prazosin hydrochloride 21187-98-4, Gliclazide 21829-25-4,  
 Nifedipine 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 26807-65-8,  
 Indapamide 29094-61-9, Glipizide 29122-68-7, Atenolol 42200-33-9,  
 Nadolol 49562-28-9, Fenofibrate 55142-85-3, Ticlopidine 56180-94-0,  
 Acarbose 56211-40-6, Torasemide 62571-86-2, Captopril 66376-36-1,  
 Alendronate 68475-42-3, Anagrelide 72432-03-2, Miglitol 72956-09-3,  
 Carvedilol 75330-75-5, Lovastatin 75847-73-3, Enalapril 76547-98-3,  
 Lisinopril 79902-63-9, Simvastatin 80830-42-8, Fentiapril  
 81093-37-0, Pravastatin 85441-61-8, Quinapril 86541-75-5, Benazepril  
 87333-19-5, Ramipril 89750-14-1, Glucagon-like peptide I 89750-14-1D,  
 Glucagon-like peptide I, mimetics 93479-97-1, Glimepiride 93957-54-1,  
 Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7,  
 Troglitazone 98048-97-6, Fosinopril 103775-10-6, Moexipril  
 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8,  
 Pioglitazone 111470-99-6, Amlodipine besylate 113665-84-2,  
 Clopidogrel 114798-26-4, Losartan 120014-06-4, Donepezil  
**122320-73-4**, Rosiglitazone 134523-00-5, Atorvastatin  
 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6,  
 Irbesartan 141758-74-9, AC2993 143443-90-7, Ifetroban 143653-53-6,  
 Abciximab 144288-97-1, TS 962 144494-65-5, Tirofiban 145599-86-6,  
 Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427  
 159183-92-3, L750355 160135-92-2, Gemopatrilat 161600-01-7  
 162011-90-7, Vioxx 166518-60-1, Avasimibe 167305-00-2, Omapatrilat  
 169319-62-4, CGS 30440 169590-42-5, Celebrex 170861-63-9, JTT-501  
 176435-10-2, LY315902 178759-95-0, MD 700 182815-44-7, Cholestagel  
 188627-80-7, Eptifibatide 196808-45-4 199113-98-9, NN-2344  
 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677  
 251572-86-8, P32/98 287714-41-4, Rosuvastatin 335149-08-1, L895645  
 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, AR-HO39242  
 335149-19-4, GW-409544 335149-23-0, NVP-DPP-728A 335149-24-1, ATL-962  
 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipyrider  
 430433-43-5, CP 644673

(therapeutic compns. also contg.; prepn. of fused pyridine derivs. as  
 HMG-CoA reductase inhibitors)

L9 ANSWER 21 OF 27 USPATFULL on STN  
 AN 2002:102031 USPATFULL  
 TI Compositions and methods for improved delivery of ionizable hydrophobic  
 therapeutic agents  
 IN Chen, Feng-Jing, Salt Lake City, UT, United States  
 Patel, Mahesh V., Salt Lake City, UT, United States  
 PA Lipocine, Inc., Salt Lake City, UT, United States (U.S. corporation)  
 PI US 6383471 B1 20020507  
 AI US 1999-287043 19990406 (9)  
 DT Utility  
 FS GRANTED  
 EXNAM Primary Examiner: Bawa, Raj  
 LREP Reed, Dianne E., Reed & Associates  
 CLMN Number of Claims: 114  
 ECL Exemplary Claim: 1  
 DRWN 0 Drawing Figure(s); 0 Drawing Page(s)  
 LN.CNT 3051  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The present invention is directed to a pharmaceutical composition  
 including a hydrophobic therapeutic agent having at least one ionizable  
 functional group, and a carrier. The carrier includes an ionizing agent

capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of preparing such compositions by providing a composition of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compositions of the invention are particularly suitable for use in oral dosage forms.

- SUMM . . . acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, gliclazide, glipizide, glybenclamide, glyburide, **glimepiride**, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, . . .
- SUMM . . . docusate, dronabinol, enalapril, enoxacin, eposartan, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, fumagillin, gabapentin, gemfibrozil, gliclazide, glipizide, glyburide, **glimepiride**, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, mesalamine, methotrexate, montelukast, naproxen, . . .
- SUMM . . . ciprofloxacin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproex, dronabinol, enoxacin, etodolac, etoposide, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, gemfibrozil, glipizide, glyburide, **glimepiride**, grepafloxacin, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lomefloxacin, lovastatin, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, . . .
- SUMM . . . one ionizable acidic functional group are: alclofenac, aspirin, atorvastatin, atovaquone, benazepril, bromfenac, celecoxib, cromoglicate, cromolyn, diclofenac, dronabinol, etodolac, fexofenadine, flurbiprofen, **glimepiride**, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, levothyroxine, lomefloxacin, naproxen, non-essential fatty acids, oxaprozin, phenytoin, pioglitazone, rabeprazole, repaglinide, teniposide, tetrahydrocannabinol, tolmetin, tretinoin, troglitazone, . . .
- SUMM . . . levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclizine, medazepam, mefloquine, melonicam, meptazinol, mercaptopurine, mesalamine, mesoridazine, **metformin**, methadone, methaqualone, methylphenidate, methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone, molindone, montelukast, morphine, moxifloxacin, nadolol, . . .
- SUMM . . . isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lansoprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, mazindol, mebendazole, mefloquine, mercaptopurine, mesalamine, **metformin**, methadone, methaqualone, methylphenidate, methysergide, metoclopramide, metoprolol, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, naratriptan, nelfinavir, nevirapine, nifedipine, nicotine, nifedipine, nimodipine, . . .
- SUMM . . . fentanyl, fexofenadine, flunarizine, fluoxetine, frovatriptan, granisetron, grepafloxacin, halofantrine, indinavir, irinotecan, isradipine, itraconazole, ketoconazole, ketotifen, lamivudine, lansoprazole, leflunomide, levofloxacin, loperamide, loratadine, **metformin**, methadone, methylphenidate, methysergide, metronidazole, miconazole, midazolam, miglitol, mitoxantrone, montelukast, naratriptan, nelfinavir, nicotine, nifedipine, nimorazole,

nizatidine, norfloxacin, ofloxacin, omeprazole, ondansetron,  
perchlorperazine, . . .

CLM What is claimed is:

. . . acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen,  
fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril,  
fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil,  
gliclazide, glipizide, glybenclamide, glyburide, **glimepiride**,  
grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan,  
isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin,  
levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin,  
meclofenamic acid, mefenamic acid, . . .

. . . . dronabinol, enalapril, enoxacin, epalrestat, eposartan, etodolac,  
etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole,  
flurbiprofen, fluvastatin, fosphenytoin, fumagillin, gabapentin,  
gemfibrozil, gliclazide, glipizide, glyburide, **glimepiride**,  
grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan,  
isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin,  
levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin,  
mesalamine, methotrexate, montelukast, naproxen, . . .

. . . . cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol,  
divalproex, dronabinol, enoxacin, epalrestat, etodolac, etoposide,  
fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin,  
fosphenytoin, gemfibrozil, glipizide, glybunde, **glimepiride**,  
grepafloxacin, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac,  
lamotrigine, levofloxacin, levothyroxine, lomefloxacin, lovastatin,  
methotrexate, montelukast, naproxen, nimesulide, non-essential fatty  
acids, norfloxacin, ofloxacin, . . .

. . . . from the group consisting of alclofenac, aspirin, atorvastatin,  
atovaquone, benazepril, bromfenac, celecoxib, cromoglicate, cromolyn,  
diclofenac, dronabinol, epalrestat, etodolac, fexofenadine,  
flurbiprofen, **glimepiride**, ibufenac, ibuprofen, isotretinoin,  
ketorolac, levothyroxine, naproxen, non-essential fatty acids,  
oxaprozin, phenytoin, pioglitazone, rabeprazole, repaglinide,  
teniposide, tetrahydrocannabinol, tolmetin, tretinoin, troglitazone,  
trovaflouxacin, . . .

. . . . levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine,  
lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol,  
mebendazole, meclizine, medazepam, mefloquine, melonicam, meptazinol,  
mercaptopurine, mesalamine, mesoridazine, **metformin**,  
methadone, methaqualone, methylphenidate, methylphenobarbital,  
methysergide, metoclopramide, metoprolol, metronidazole, mianserin,  
miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone,  
molindone, montelukast, morphine, moxifloxacin, nadolol, . . .

. . . . isradipine, itraconazole, ketoconazole, ketotifen, labetalol,  
lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril,  
lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, mazindol,  
mebendazole, mefloquine, mercaptopurine, mesalamine, **metformin**  
, methadone, methaqualone, methylphenidate, methysergide,  
metoclopramide, metoprolol, metronidazole, miconazole, midazolam,  
miglitol, minoxidil, mitoxantrone, montelukast, naratriptan, nelfinavir,  
nevirapine, nicardipine, nicotine, nifedipine, nimodipine, . . .

. . . . fentanyl, fexofenadine, flunarizine, fluoxetine, frovatriptan,  
granisetron, grepafloxacin, halofantrine, indinavir, irinotecan,  
isradipine, itraconazole, ketoconazole, ketotifen, lamivudine,  
lanosprazole, leflunomide, levofloxacin, loperamide, loratadine,  
**metformin**, methadone, methylphenidate, methysergide,  
metronidazole, miconazole, midazolam, miglitol, mitoxantrone,  
montelukast, naratriptan, nelfinavir, nicotine, nifedipine, nimorazole,  
nizatidine, norfloxacin, ofloxacin, omeprazole, perchlorperazine,  
phenbenzamine, . . .

IT 74504-64-6, Polyglyceryl laurate 75330-75-5, Lovastatin 75695-93-1,  
Isradipine 75706-12-6, Leflunomide 75847-73-3, Enalapril 76009-37-5

76547-98-3, Lisinopril 76584-70-8 76824-35-6, Famotidine  
 76963-41-2, Nizatidine 77671-31-9, Enoximone 78273-80-0, Roxatidine  
 79617-96-2, Sertraline 79665-93-3, Nikkol Decaglyn 10 79665-94-4  
 79794-75-5, Loratadine 80214-83-1, Roxithromycin 81093-37-0,  
 Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin  
 82159-09-9, Epalrestat 82419-36-1, Ofloxacin 82626-48-0, Zolpidem  
 82664-20-8, Flurithromycin 83366-66-9, Nefazodone 83799-24-0,  
 Fexofenadine 83881-51-0, Cetirizine 83905-01-5, Azithromycin  
 84057-84-1, Lamotrigine 84449-90-1, Raloxifene 84625-61-6,  
 Itraconazole 85441-61-8, Quinapril 85721-33-1, Ciprofloxacin  
 86386-73-4, Fluconazole 86541-75-5, Benazepril 87718-67-0,  
 Spiramycins 87848-99-5, Acrivastine 88150-42-9, Amlodipine  
 89778-26-7, Toremifene 91161-71-6, Terbinafine 91374-21-9, Ropinirole  
 91714-94-2, Bromfenac 93106-60-6, Enrofloxacin 93390-81-9,  
 Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride  
 93957-54-1, Fluvastatin 94423-19-5 94555-53-0 95233-18-4,  
 Atovaquone 97322-87-7, Troglitazone 97682-44-5, Irinotecan  
 98048-97-6, Fosinopril 98079-51-7 98913-68-9, Pentaerythritol  
 isostearate 99614-02-5, Ondansetron 100986-85-4, Levofloxacin  
 101828-21-1, Butenafine 102051-00-3, Nikkol Decaglyn 30 103177-37-3,  
 Pranlukast 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan  
 104632-26-0, Pramipexole 105979-17-7, Benidipine 106133-20-4,  
 Tamsulosin 106266-06-2, Risperidone 106392-12-5, Polyoxyethylene-  
 polyoxypropylene block copolymer 106650-56-0, Sibutramine  
 107753-78-6, Zafirlukast 109889-09-0, Granisetron 110871-86-8,  
 Sparfloxacin 111025-46-8, Pioglitazone 111974-69-7, Quetiapine  
 113665-84-2, Clopidogrel 114798-26-4, Losartan 115103-54-3, Tiagabine  
 115956-12-2, Dolasetron 117976-89-3, Rabeprazole 119914-60-2,  
 Grepafloxacin 120014-06-4, Donepezil 121548-04-7, Gelucire 44/14  
 121548-05-8, Gelucire 50/13 121679-13-8, Naratriptan  
 122320-73-4, Rosiglitazone 123948-87-8, Topotecan  
 124937-51-5, Tolterodine 127779-20-8, Saquinavir 129497-78-5,  
 Verteporfin 129618-40-2, Nevirapine 132539-06-1, Olanzapine  
 132875-61-7, Remifentanyl 133040-01-4, Eprosartan 133248-87-0,  
 Maisine 134308-13-7, Tolcapone 134523-00-5, Atorvastatin  
 134678-17-4, Lamivudine 135062-02-1, Repaglinide 136470-78-5,  
 Abacavir 136817-59-9, Delavirdine 137862-53-4, Valsartan  
 138402-11-6 139264-17-8, Zolmitriptan 139481-59-7, Candesartan  
 139755-83-2, Sildenafil 144034-80-0, Rizatriptan 144494-65-5,  
 Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin  
 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 150372-93-3,  
 Glycerol L 150378-17-9, Indinavir 151096-09-2, Moxifloxacin  
 154598-52-4, Efavirenz 155213-67-5, Ritonavir 156259-68-6, Capmul MCM  
 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7,  
 Nelfinavir 161814-49-9, Amprenavir 169590-42-5, Celecoxib  
 185069-68-5, Polyglyceryl oleate stearate 211365-88-7, Nikkol BPS-30  
 301206-59-7 301524-91-4, Captex 810  
 (pharmaceutical compns. contg. hydrophobic therapeutic agents and  
 carriers contg. ionizing agents and surfactants and triglycerides)

L9 ANSWER 22 OF 27 USPATFULL on STN  
 AN 2002:67275 USPATFULL  
 TI Combination therapeutic compositions and method of use  
 IN Jaen, Juan C., Burlingame, CA, UNITED STATES  
 Chen, Jin-Long, Foster City, CA, UNITED STATES  
 PI US 2002037928 A1 20020328  
 AI US 2001-847887 A1 20010502 (9)  
 PRAI US 2000-201613P 20000503 (60)  
 DT Utility  
 FS APPLICATION  
 LREP TOWNSEND AND TOWNSEND AND CREW, TWO EMBARCADERO CENTER, EIGHTH FLOOR,  
 SAN FRANCISCO, CA, 94111-3834

CLMN Number of Claims: 51  
ECL Exemplary Claim: 1  
DRWN 7 Drawing Page(s)  
LN.CNT 1692

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides pharmaceutical compositions and methods for the treatment of diabetes mellitus using combination therapy. The compositions relate to a compound of Formula I and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, .alpha.-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of compound of Formula I with antidiabetic agent where the two components are delivered in a simultaneous manner, where the compound of Formula I is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound of Formula I.

SUMM . . . For most diabetic patients, treatment involves some form of insulin therapy. In addition, IDDM patients may receive a biguanide (e.g., **metformin**) to enhance the insulin utilization by peripheral tissues. NIDDM patients are often treated with a combination of insulin, a sulfonylurea. . . . glitazone compounds (rosiglitazone and pioglitazone) were approved in the United States for the treatment of NIDDM patients in combination with **metformin**.

SUMM . . . in the treatment of hyperglycemia by mechanisms that are not well understood. The best known agents of this type include **metformin**, phenformin and buformin. Unlike the sulfonylureas, **metformin** does not induce release of insulin from the pancreas. It is thought that its effects are mediated by increasing insulin. . . .

DETD . . . GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2; sulfonylureas and analogs, including, but not limited to, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glipizide, **glimepiride**, repaglinide and meglitinide; biguanides, including, but not limited to, **metformin**, phenformin and buformin.

DETD . . . Preferred sulfonylureas suitable for use in the present invention include, but are not limited to, acetohexamide, chlorpropamide, glyburide, glipizide, gliclazide, **glimepiride**, gliquidone, glisoxepid, glibomuride, gliamilide, glibomuride, glicetanile, gliflumide, glymidine, glyparamide, tolpyrramide, glyhexamide, phenbutamide, tolazamide, tolbutamide and tolcyclamide. Those of skill in. . . .

DETD . . . in the treatment of hyperglycemia. Preferred biguanides suitable for use in the present invention include, but are not limited to, **metformin**, phenformin and buformin. Unlike the sulfonylureas, **metformin** does not induce release of insulin from the pancreas. Without being bound by any particular theory, it is thought that. . . .

DETD . . . and aryl-heteroalkyl. Preferably, R, R' and R" are each independently selected from hydrogen, (C.sub.1-C.sub.3)alkyl and aryl-(C.sub.1-C.sub.3) alkyl. Preferred biguanides include **metformin**, buformin, etoformin and phenformin.

CLM What is claimed is:

. . . claim 2, wherein said sulfonyl urea is a member selected from the group consisting of acetohexamide, chlorpropamide, glyburide, glipizide, gliclazide, **glimepiride**, gliquidone, glisoxepid, glibomuride, gliamilide, glicetanile, gliflumide, glymidine, glyparamide, tolpyrramide, glyhexamide, phenbutamide, tolazamide, tolbutamide and tolcyclamide.

4. The pharmaceutical composition of claim 2, wherein said biguanide is a member selected from the group consisting of **metformin**,

buformin, etoformin and phenformin.

IT 50-18-0, Cyclophosphamide 50-78-2, Aspirin 52-53-9, Verapamil  
53-03-2, Prednisone 53-86-1, Indomethacin 55-63-0, Nitroglycerin  
56-03-1D, Biguanide, derivs. 59-05-2, Methotrexate 59-67-6, Niacin,  
biological studies 64-77-7, Tolbutamide 64-86-8, Colchicine  
86-54-4, Hydralazine 94-20-2, Chlorpropamide 114-07-8, Erythromycin  
114-86-3, Phenformin 124-94-7, Triamcinolone 154-93-8, Carmustine  
300-62-9, Amphetamine 315-30-0, Allopurinol 339-44-6, Glymidine  
451-71-8, Glyhexamide 518-28-5, Podophyllotoxin 525-66-6, Propranolol  
657-24-9, Metformin 664-95-9, Tolcyclamide 692-13-7, Buformin  
968-81-0, Acetohexamide 1156-19-0, Tolazamide 1406-18-4, Vitamin E  
3149-00-6, Phenbutamide 4205-90-7, Clonidine 4759-48-2, Isotretinoin  
5581-42-0, Glyparamide 5588-38-5, Tolpyrramide 9004-10-8, Insulin,  
biological studies 10238-21-8, Glyburide 10540-29-1, Tamoxifen  
13010-20-3D, Nitrosourea, metal derivs. 13598-36-2D, Phosphonic acid,  
alkylidenebis- derivs. 15663-27-1, Cisplatin 19216-56-9, Prazocine  
21187-98-4, Gliclazide 23214-92-8, Doxorubicin 24455-58-1,  
Glicetanile 25046-79-1, Glisoxepid 25812-30-0, Gemfibrozil  
26944-48-9, Glibornuride 29094-61-9, Glipizide 33069-62-4, Paclitaxel  
33342-05-1, Gliquidone 33419-42-0, Etoposide 35273-88-2, Gliflumide  
42399-41-7, Diltiazem 45086-03-1, Etoformin 50925-79-6, Colestipol  
51876-98-3, Gliamilide 56180-94-0, Acarbose 59865-13-3, Cyclosporine  
62571-86-2, Captopril 72432-03-2, Miglitol 74772-77-3, Ciglitazone  
79902-63-9, Simvastatin 80879-63-6, Emiglitate 83480-29-9, Voglibose  
93479-97-1, Glimepiride 97322-87-7, Troglitazone 103787-97-9, BM  
131246 103788-05-2, AD-5075 104343-33-1, MDL-25637 104987-11-3,  
FK-506 106650-56-0, Sibutramine 109229-58-5, Englitazone  
111025-46-8, Pioglitazone 114798-26-4, Losartan 120014-06-4,  
Donepezil 122320-73-4, Rosiglitazone 127214-23-7, Camiglibose  
141200-24-0, Darglitazone 170861-63-9, JTT-501 199914-96-0  
371968-35-3D, derivs.  
(benzene compds. in combination therapy for diabetes and  
diabetes-related disorders)

L9 ANSWER 23 OF 27 USPATFULL on STN

AN 2002:27439 USPATFULL

TI Treatment of diabetes with thiazolidinedione, insulin secretagogue and  
diguamide

IN Buckingham, Robin Edwin, Wel Wyn Garden City, UNITED KINGDOM

Smith, Stephen Alistair, Bramfield, UNITED KINGDOM

PA SmithKline Beecham p.l.c. (non-U.S. corporation)

PI US 2002016287 A1 20020207

AI US 2001-939470 A1 20010824 (9)

RLI Continuation of Ser. No. US 1999-446039, filed on 15 Dec 1999, PENDING A  
371 of International Ser. No. WO 1999-GB9802110, filed on 28 Jan 1999,  
UNKNOWN

PRAI GB 1997-15295 19970718

DT Utility

FS APPLICATION

LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box  
1539, King of Prussia, PA, 19406-0939

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 479

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment of diabetes mellitus and conditions  
associated with diabetes mellitus in a mammal, which method comprises  
administering an effective non-toxic and pharmaceutically acceptable  
amount of an insulin sensitiser, an insulin secretagogue and a biguanide  
antihyperglycaemic agent, to a mammal in need thereof; and composition

for use in such method.

SUMM . . . as antihyperglycaemic agents and are used in the treatment of Type 2 diabetes). Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0004] Biguanide antihyperglycaemic agents are commonly used in the treatment of Type 2 diabetes). 1,1-Dimethylbiguanidine (or **Metformin**) is an example of a biguanide antihyperglycaemic agent.

SUMM [0020] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0023] A suitable biguanide antihyperglycaemic agent is **metformin**, buformin or phenformin, especially **metformin**.

DETD [0066] With regard to the biguanide antihyperglycaemic agents, suitable dosages of **metformin** include up to 3000 mg per day, in unit doses of 500 mg (for example two or three times per day) or 850 mg (for example two times per day), one example of a dosage for **metformin** is 500 mg once building to five times per day.

CLM What is claimed is:

2. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glycopyramide, glycylamide or repaglinide.

3. A method according to claim 1, wherein the biguanide is **metformin**, buformin or phenformin.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glycopyramide, glycylamide or repaglinide.

17. A composition according to claim 1, wherein the biguanide is **metformin**, buformin or phenformin.

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 114-86-3, Phenformin 339-43-5, Carbutamide 631-27-6, Glycopyramide 657-24-9, Metformin 664-95-9, Glycylamide 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 74772-77-3, Ciglitazone 93479-97-1, Glimepiride 97322-87-7, Troglitazone 109229-58-5, Englitazone 111025-46-8, Pioglitazone **122320-73-4** 135062-02-1, Repaglinide 155141-29-0  
(thiazolidinedione, insulin secretagogue, and biguanide for diabetes treatment)

L9 ANSWER 24 OF 27 USPATFULL on STN

AN 2002:22432 USPATFULL

TI Synergistic effect of a sulfonylurea and/or non-sulfonylurea Kchannel blocker, and a phosphodiesterase 3 type inhibitor

IN Fryburg, David A., East Lyme, CT, UNITED STATES  
Parker, Janice C., Ledyard, CT, UNITED STATES

PI US 2002013268 A1 20020131  
US 6610746 B2 20030826

AI US 2001-829874 A1 20010410 (9)

PRAI US 2000-196728P 20000413 (60)

DT Utility

FS APPLICATION

LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340

CLMN Number of Claims: 25

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 1475

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods of treating non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance, the methods comprising the step of administering to a patient having or at risk of having non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance a synergistic amount of: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also provides kits and pharmaceutical compositions that comprise: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also relates to kits and pharmaceutical compositions that comprise 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; 2) a cAMP phosphodiesterase type 3 inhibitor; and 3) an additional compound useful for the treatment of non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance.

SUMM . . . a more preferred embodiment of the kits, the second compound is selected from LysPro insulin, GLP-1 (7-37) (insulinotropin), GLP-1 (7-36)-NH.sub.2, **metformin**, phenformin, buformin, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan, linoglriride, ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone, clomoxir, etomoxir, acarbose, miglitol, emiglitate, . . .

SUMM [0055] In another preferred embodiment of the methods, kits, and pharmaceutical compositions, the sulfonylurea is glyburide, chlorpropamide, glibenclamide, glipizide, gliclazide, **glimepiride**, tolbutamide, acetohexamide, or tolazamide.

DETD [0120] Preferred compounds from the above classes include: LysPro insulin; GLP-1 (7-37) (insulinotropin); GLP-1 (7-36)-NH.sub.2; **metformin**; phenformin; buformin; midaglizole; isaglidole; deriglidole; idazoxan; efaroxan; fluparoxan; linoglriride; ciglitazone; pioglitazone; englitazone; troglitazone; darglitazone; rosiglitazone; clomoxir; etomoxir; acarbose; miglitol; emiglitate; . . .

CLM What is claimed is:

3. The method of claim 1 wherein the sulfonylurea is glyburide, chlorpropamide, glibenclamide, glipizide, gliclazide, **glimepiride**, tolbutamide, acetohexamide, or tolazamide.

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 114-86-3, Phenformin 458-24-2, Fenfluramine 657-24-9, Metformin 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 2295-31-0D, Thiazolidinedione, derivs. 7440-62-2D, Vanadium, complexes 9004-10-8D, Insulin, analogs 10238-21-8, Glyburide 21187-98-4, Gliclazide 23602-78-0, Benfluorex 28299-33-4D, Imidazoline, derivs. 29094-61-9, Glipizide 37353-31-4,

Vanadate 51037-30-0, Acipimox 56180-94-0, Acarbose 60719-84-8,  
 Amrinone 66529-17-7, Midaglizole 68550-75-4, Cilostamide  
 72432-03-2, Miglitol 73384-60-8 73963-72-1, Cilostazol 74150-27-9,  
 Pimobendan 74772-77-3, Ciglitazone 75358-37-1, Linoglliride  
 77671-31-9, Enoximone 78415-72-2, Milrinone 79944-58-4, Idazoxan  
 80879-63-6, Emiglitate 81840-15-5, Vesnarinone 83480-29-9, Voglibose  
 84243-58-3, Imazodan 86615-96-5, BRL 35135 88431-47-4, Clomoxir  
 89197-32-0, Efaroxan 90505-66-1, Ro 16-8714 90730-96-4, BRL 37344  
 93479-97-1, Glimepiride 94192-59-3, Lixazinone 97322-87-7,  
 Troglitazone 100510-33-6, Adibendan 100643-96-7, Indolidan  
 102669-89-6, Saterinone 104343-33-1, MDL-25637 105182-45-4,  
 Fluparoxan 105816-04-4, Nateglinide 106612-94-6, Insulinotropin  
 (human) 107444-51-9 109229-58-5, Englitzazone 110605-64-6,  
 Isaglidole 111025-46-8, Pioglitazone 112018-01-6, Bemoradan  
 115344-47-3, Siguazodan **122320-73-4**, Rosiglitazone  
 122575-28-4, Naglivan 122830-14-2, Deriglidole 124083-20-1, Etomoxir  
 127214-23-7, Camiglibose 129689-30-1, ICI D7114 130714-47-5, WAG 994  
 133107-64-9 135062-02-1, Repaglinide 138908-40-4, CL316243  
 141200-24-0, Darglitazone 187887-46-3, Symlin 335149-21-8, AC2993  
 (sulfonylurea and/or non-sulfonylurea K<sup>+</sup> ATP channel blocker and  
 phosphodiesterase 3 type inhibitor synergism for treatment of  
 non-insulin-dependent diabetes or other conditions)

L9 ANSWER 25 OF 27 USPATFULL on STN  
 AN 2001:226658 USPATFULL  
 TI Pharmaceutical composition for the treatment of diabetes  
 IN Odaka, Hiroyuki, Kobe, Japan  
 Yamane, Masahiro, Suita, Japan  
 PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)  
 PI US 6329403 B1 20011211  
 WO 20000000195 20000106  
 AI US 1999-380059 19990825 (9)  
 WO 1999-JP3496 19990629  
 19990825 PCT 371 date  
 19990825 PCT 102(e) date  
 PRAI JP 1998-183700 19980630  
 DT Utility  
 FS GRANTED  
 EXNAM Primary Examiner: Cook, Rebecca  
 LREP Chao, Mark, Ramesh, Elaine M.  
 CLMN Number of Claims: 19  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 1134  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB A pharmaceutical composition which comprises an insulin sensitizer in  
 combination with an anorectic, which is useful as an agent for  
 preventing or treating diabetes.  
 SUMM . . . glycopyramide or its ammonium salt, glibenclamide, gliclazide,  
 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide,  
 gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide,  
 glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride  
 , etc.  
 SUMM Examples of the biguanides include phenformin, metformin,  
 buformin, etc.  
 IT 97322-87-7, Troglitazone **122320-73-4**, Rosiglitazone  
 155141-29-0, Rosiglitazone maleate 170861-63-9  
 (insulin sensitizer in combination with an anorectic for the treatment  
 of diabetes)

L9 ANSWER 26 OF 27 USPATFULL on STN  
 AN 2001:139544 USPATFULL

*3 diff  
 marks  
 to original  
 + not  
 dated  
 or  
 initial*

TI Use of organic compounds  
 IN Guitard, Christiane, Hegenheim, France  
 Muller, Beate, Hanner, Germany, Federal Republic of  
 Emmons, Rebecca, Riehen, Switzerland  
 PI US 2001016586 A1 20010823  
 AI US 2000-731139 A1 20001206 (9)  
 PRAI EP 1999-125761 19991223  
 DT Utility  
 FS APPLICATION  
 LREP THOMAS HOXIE, NOVARTIS CORPORATION, PATENT AND TRADEMARK DEPT, 564  
 MORRIS AVENUE, SUMMIT, NJ, 079011027  
 CLMN Number of Claims: 10  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 747  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to the use of a hypolipidemic agent or a  
 pharmaceutically acceptable salt thereof for the manufacture of a  
 medicament for the prevention or delay of the progression to overt  
 diabetes, especially type 2, prevention or reduction of microvascular  
 complications (eg, retinopathy, neuropathy, nephropathy), prevention or  
 reduction of excessive cardiovascular morbidity (eg, myocardial  
 infarction, arterial occlusive disease, atherosclerosis and stroke) and  
 cardiovascular mortality, prevention of cancer and reduction of cancer  
 deaths. Additionally, the invention relates to the use of a treatment  
 for diseases and conditions that are associated with IGM, IGT or IFG.  
 SUMM [0019] An appropriate biguanide is, for example, **metformin** or,  
 if appropriate, a pharmaceutically acceptable salt thereof, especially  
 the hydrochloride thereof.  
 SUMM . . . Insulin secretion enhancers furthermore include the  
 representatives of the new generation of SUs such as calcium  
 (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)-propionate  
 dihydrate (KAD-1229) and **glimepiride** (Hoe 490); and in free or  
 pharmaceutically acceptable salt form.  
 SUMM [0026] A preferred insulin secretion enhancer is repaglinide and  
**metformin**, most preferred is nateglinide.  
 SUMM . . . the present invention preferably those that are designated as  
 preferred hypoglycemic agents, that are most preferably selected from  
 nateglinide, repaglinide, **metformin**, pioglitazone,  
 rosiglitazone, troglitazone, 1-{2-[(5-cyanopyridin-2-  
 yl)amino]ethylamino}acetyl-2(S)-cyano-pyrrolidine, and  
 (S)1-[(3-hydroxy-1-adamantyl)amino]-acetyl-2-cyano-pyrrolidine, or, if  
 appropriate, in each case, a pharmaceutically acceptable salt thereof.  
 SUMM . . . tablets of repaglinide in doses of 0.5 mg, 1 mg or 2 mg of the  
 active ingredient or tablets of **metformin** in doses of 500 mg  
 or 850 mg of the active ingredient may be taken Likewise these doses may  
 also. . .  
 IT 56-03-1D, Biguanide, derivs. 103-82-2D, Phenylacetic acid, derivs.  
 33342-05-1, Gliquidone 97322-87-7, Troglitazone 105816-04-4,  
 Nateglinide 111025-46-8, Pioglitazone **122320-73-4**,  
 Rosiglitazone 135062-02-1, Repaglinide  
 (hypoglycemic agent for treating impaired glucose metab.)  
 L9 ANSWER 27 OF 27 USPATFULL on STN  
 AN 2000:1892 USPATFULL  
 TI Combinations for diabetes  
 IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States  
 PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S.  
 corporation)  
 PI US 6011049 20000104  
 AI US 1998-189132 19981109 (9)  
 RLI Continuation-in-part of Ser. No. US 1997-970057, filed on 13 Nov 1997,

now patented, Pat. No. US 5859037  
PRAI US 1997-38224P 19970219 (60)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Jordan, Kimberly  
LREP Ashbrook, Charles W.  
CLMN Number of Claims: 16  
ECL Exemplary Claim: 1  
DRWN 12 Drawing Figure(s); 12 Drawing Page(s)  
LN.CNT 974

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combinations of a glitazone antidiabetic agent and a biguanide antidiabetic agent, and optionally a sulfonylurea antidiabetic agent, are useful for treating diabetes mellitus and improving glycemic control.

SUMM . . . treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone, together with a biguanide antidiabetic agent such as **metformin**, or simply a glitazone together with a biguanide. The clinical data presented herein establishes the unexpected biological benefits achievable with. . .

SUMM . . . sulfonylureas to be employed in the combinations of this invention are glyburide, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, **glimepiride**, phenbutamide, and tolcyclamide.

SUMM A typical biguanide is **metformin**. It typically is used clinically as a pharmaceutically acceptable salt, preferably the hydrochloride salt. A commercial form of **metformin** hydrochloride is available, and its chemical name is N,N-dimethylimidodicarbonimidic diamide hydrochloride. **Metformin** hydrochloride has the structural formula ##STR7## As used herein, "**metformin**" means the base compound as well as its pharmaceutically acceptable salts. **Metformin** is used clinically to manage NIDDM, particularly in patients who are not effectively treated with a sulfonylurea. While it is. . .

DRWD FIG. 8 Change in fasting plasma glucose (FPG) (±SEM) during **metformin** and troglitazone monotherapy and during **metformin** and troglitazone combination therapy.

DRWD FIG. 9 Changes in FPG and post-prandial glucose (PPG) (±SEM) at 3 months of monotherapy of **metformin** and of troglitazone.

DRWD FIG. 10 (A) Mean percent change in endogenous glucose production (EGP) after 3 months of monotherapy of **metformin** and of troglitazone. (B) Mean percent change in glucose disposal rates (GDR) under hyperinsulinemic clamp conditions after 3 months of monotherapy of **metformin** and of troglitazone.

DRWD FIG. 11 Changes in FPG and PPG after 3 months monotherapy of **metformin** and of troglitazone, and after an additional 3 months of combination therapy (**metformin** and troglitazone).

DRWD FIG. 12 Change in hemoglobin A1c (HbA<sub>1c</sub>) (±SEM) during 3 months of monotherapy of **metformin** and troglitazone and after an additional 3 months of combination therapy (**metformin** and troglitazone).

DETD . . . glitazone is pioglitazone, and it will be employed at doses of about 50 mg to about 200 mg per day. **Metformin** hydrochloride will be administered at doses of about 300 mg to about 2000 mg per day. It is available commercially. . .

DETD Typical combinations to be employed according to this invention thus include troglitazone plus **metformin**, and troglitazone plus **metformin** plus a sulfonylurea such as glyburide. Another typical and preferred combination is rosiglitazone plus **metformin**, and rosiglitazone plus **metformin** plus a ;sulfonylurea such as glyburide. Still another preferred combination is pioglitazone plus **metformin**, and pioglitazone plus **metformin** plus a

sulfonylurea such as glyburide. These combinations produce better than expected control of NIDDM.

DETD The invention provides compositions of antidiabetic agents, for example, **metformin** and a glitazone, as well as **metformin**, a sulfonylurea and a glitazone, and a method of treating diabetes and controlling glycemic conditions comprising administering to a patient in need of treatment an effective amount of **metformin** and a glitazone, or **metformin**, a sulfonylurea and an effective amount of a glitazone. When the sulfonylurea and glitazone are formulated together, the compositions will. . . troglitazone. Such combination will be administered to an adult patient about once each day to achieve a desired glycemic control. **Metformin** can be combined directly with a glitazone such as troglitazone. Typical doses will be about 500 mg of **metformin** and about 300 to 600 mg of troglitazone. A typical three-way composition includes 12 mg of glyburide, 400 mg of troglitazone, and 500 mg of **metformin**.

DETD The glitazones can also be utilized in combination with a biguanide such as **metformin**, as well as in combination with a biguanide plus a sulfonylurea. Several clinical trials have established the unexpected biological efficacy that is achieved with a combination of troglitazone and **metformin**, as well as troglitazone, **metformin**, and glyburide.

DETD In one clinical trial, patients were treated with monotherapy of **metformin** or troglitazone for 3 months, followed by combination therapy for 3 months. Twenty-nine patients diagnosed as having NIDDM were randomized. Fifteen subjects received **metformin** monotherapy, 1000 mg orally twice a day for 3 months. A group of 14 subjects were dosed orally with 400. . .

DETD TABLE 5

#### Baseline Characteristics of Subjects Who Completed the 3-Month Monotherapy Phase of the Trial

	<b>Metformin</b>		Troglitazone	
	Group (n = 15)		Group (n = 13)	
				p =
Age (years)	51	(.+- .3)	53	(.+- .2)
				0.32 (NS)

Weight (kg) 99. . .

DETD After the initial 3-month period of monotherapy, the remaining subjects were dosed with a combination of **metformin** and troglitazone (1000 mg **metformin** BID, 400 mg troglitazone QD) for an additional 3-month period.

DETD At 3 months on monotherapy, both **metformin** and troglitazone caused a 20% decrease from baseline of FPG; 58 mg/dL and 54 mg/dL, respectively (FIG. 8). HbA<sub>1c</sub> levels did not change significantly with either drug. Mean post-prandial glucose decreased about 25% for both groups (**metformin** 87 mg/dL, troglitazone 83 mg/dL), as shown in FIG. 9. Post-prandial circulating insulin and C-peptide decreases were insignificantly different from. . . mg/m.sup.2 /min (18%) in the metformintreated group (FIG. 10A), while troglitazone had no effect on EGP (FIG. 10B). In contrast, **metformin** caused less than 27% increase in glucose disposal rate (GDP) (240 to 272 mg/m.sup.2 /min) (FIG. 10B), whereas troglitazone caused. . .

DETD When the study patients were given the combination of **metformin** and troglitazone for 3 months, dramatic and unexpected effects were observed. Fasting plasma glucose levels decreased an additional 18% (41. . .

DETD The foregoing study establishes that the combination of **metformin** and troglitazone causes a clinically significant and

unexpected further lowering of both fasting and post-prandial glucose compared to either agent. . . .

DETD . . . . when using a three-way combination of biguanide, sulfonylurea, and glitazone. A clinical trial was carried out assessing the effects of **metformin**, glyburide, and troglitazone when compared to a typical treatment regimen of glyburide and **metformin**. Two hundred NIDDM patients were enrolled in a double-blind, randomized, placebo-controlled multicenter study. All enrolled patients had compromised glycemic control. . . . treated with a sulfonylurea (comparable in dosage to at least 20 mg of glyburide) and at least 1500 mg of **metformin** daily. Of the 200 patients enrolled, 178 completed the 24-week trial. The study population consisted of 57% males, 43% females,. . . . the start of the trial, 101 patients received oral dosing of troglitazone (400 mg once daily), a sulfonylurea (SU), and **metformin**. The control group of 99 subjects received a sulfonylurea and **metformin**. The primary efficacy parameter measured was HbA.sub.1c. Secondary efficacy parameters were FSG, C-peptide, serum total insulin, BMI weight, triglycerides, total. . . .

DETD TABLE 6

Changes From Baseline at 24 Weeks			
	SU +	SU + <b>Metformin</b> +	Adjusted
		<b>Metformin</b>	
		Troglitazone	Difference
HbA.sub.1c	+0.1	-1.3	(p < 0.001)
			-1.4
FPG	+6	-42	(p < 0.001)
			-48
Circulating Insulin			
	+1.4	-2.8	(p < 0.001)

DETD . . . . reduction in FPG, showing the unexpectedly fast onset of action achieved with the triple combination, and the synergy associated with **metformin**, sulfonylurea, and glitazone. This represents good glycemic control in about one-half the time period normally observed in clinical settings using. . . . and biguanide. Equally surprising was the dramatic reduction in endogenous insulin (19%) caused by the triple combination. Moreover, while the sulfonylurea/**metformin** combination had no effect on C-peptide levels, the triple combination of sulfonylurea/biguanide/glitazone caused a 7% reduction. Similarly, while the sulfonylurea/**metformin** treated group had an increase in triglycerides of 43 mg/dL, the sulfonylurea/glitazone/biguanide combination caused a reduction of 36 mg/dL.

CLM What is claimed is:

3. A composition of claim 1 wherein the biguanide is **metformin**

4. A synergistic composition comprising from about 100 mg to about 1000 mg of troglitazone, from about 3 mg to about 250 mg of glyburide, and from about 300 mg to about 2000 mg of **metformin**.

. . . . about 3 mg to about 250 mg of a sulfonylurea, and from about 300 mg to about 2000 mg of **metformin**.

. . . . about 3 mg to about 250 mg of a sulfonylurea, and from about 300 mg to about 2000 mg of **metformin**.

10. A method according to claim 8 wherein the biguanide is **metformin**.

14. A method of treating diabetes by administering to a patient in need of treatment from about 5 mg to about 10 mg of rosiglitazone together with from about 300 mg to about 2000 mg of **metformin** and from about 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment. . .

. . . about 100 mg to about 1000 mg of troglitazone together with from about 300 mg to about 2000 mg of **metformin** and from about 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment. . .

. . . about 50 mg to about 200 mg of pioglitazone together with from about 300 mg to about 2000 mg of **metformin** and from about 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment. . .

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2,  
Chlorpropamide 451-71-8, Glyhexamide 657-24-9, Metformin 664-95-9,  
Tolcyclamide 968-81-0, Acetohexamide 1156-19-0, Tolazamide  
3149-00-6, Phenbutamide 10238-21-8, Glyburide 21187-98-4, Gliclazide  
25046-79-1, Glisoxepid 26944-48-9, Glibornuride 29094-61-9, Glipizide  
33342-05-1, Gliquidone 97322-87-7, Troglitazone 111025-46-8,  
Pioglitazone **122320-73-4**, Rosiglitazone  
(combinations of glitazones, biguanides, and optional sulfonylureas for  
diabetes treatment)